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(54) Title: MAMMALIAN GENES; RELATED REAGENTS AND METHODS

(57) Abstract: Nucleic acids encoding mammalian, e.g., primate or rodent, genes, purified proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are provided.

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MAMMALIAN GENES; RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

5 The present invention relates to compositions and methods for affecting mammalian physiology, including morphogenesis or immune system function. In particular, it provides nucleic acids, proteins, and antibodies which regulate development and/or the immune system. Diagnostic and therapeutic uses of these materials are also disclosed.

BACKGROUND OF THE INVENTION

10 Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired
15 protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host. See, e.g., Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY.

For some time, it has been known that the mammalian immune response is based on a
20 series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play
25 critical roles in controlling these cellular interactions. The interferons are generally considered to be members of the cytokine family. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

30 Lymphokines apparently mediate cellular activities in a variety of ways. See, e.g., Paul (ed. 1998) Fundamental Immunology 4th ed., Lippincott; and Thomson (ed. 1998) The

Cytokine Handbook 3d ed., Academic Press, San Diego. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are
5 necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of
10 various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes interact with many other cell types.

One means to modulate the effect of a cytokine upon binding to its receptor, and therefore potentially useful in treating inappropriate immune responses, e.g., autoimmune, inflammation,
15 sepsis, and cancer situations, is to inhibit the receptor signal transduction. In order to characterize the structural properties of a cytokine receptor in greater detail and to understand the mechanism of action at the molecular level, purified receptor will be very useful. The receptors provided herein, by comparison to other receptors or by combining structural components, will provide further understanding of signal transduction induced by ligand binding.

20 An isolated receptor gene should provide means to generate an economical source of the receptor, allow expression of more receptors on a cell leading to increased assay sensitivity, promote characterization of various receptor subtypes and variants, and allow correlation of activity with receptor structures. Moreover, fragments of the receptor may be useful as agonists or antagonists of ligand binding. See, e.g., Harada, et al. (1992) J. Biol.
25 Chem. 267:22752-22758. Often, there are at least two critical subunits in the functional receptor. See, e.g., Gonda and D'Andrea (1997) Blood 89:355-369; Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007; Drachman and Kaushansky (1995) Curr. Opin. Hematol. 2:22-28; Theze (1994) Eur. Cytokine Netw. 5:353-368; and Lemmon and
Schlessinger (1994) Trends Biochem. Sci. 19:459-463. Other receptor types, e.g., TLR-like,
30 will similarly be useful.

Likewise, identification of novel ligands will be useful. Members of the tumor necrosis factor (TNF) family and transforming growth factor (TGF) family of ligands have identified physiological effects.

Finally, genes which exhibit disease associated expression patterns will be useful in
5 diagnostic or other uses. The molecular diagnostic utility may be applied to identify patients who will be responsive to particular therapies, or to predict responsiveness to treatment.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their receptors, including ones similar to lymphokines, should contribute to new therapies for a wide range of degenerative or abnormal conditions which directly or indirectly
10 involve development, differentiation, or function, e.g., of the immune system and/or hematopoietic cells. Moreover, novel markers will be useful in molecular diagnosis or therapeutic methods. In particular, the discovery and understanding of novel receptors or lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. The present invention provides these and related
15 compounds, and methods for their use.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1C show a sequence alignment of related IFN receptor family members.
20 Tissue Factor is SEQ ID NO: 4; hIFN α R is SEQ ID NO: 5; CRF2-4 is SEQ ID NO: 6; cytor x is SEQ ID NO: 7; and cytor7 is SEQ ID NO: 8.

Figure 2 shows an alignment of TNF-x and TNF-y polypeptides (SEQ ID NO:9, 11, and 13); p is primate, r is rodent.

Figures 3A-3E show an alignment of primate and rodent TLR-like protein sequences.

25 Figure 4 shows an Alignment of primate and rodent 5685C6 polypeptide sequences.

Figure 5 shows an alignment of Claudin homologs: D2 (SEQ ID NO:34); D8 (SEQ ID NO:37); D17 (SEQ ID NO:39); D7.2 (SEQ ID NO:41).

Figures 6A-6E show an alignment of Schlafen homologs: schlafen B (SEQ ID NO:43); schlafen C (SEQ ID NO:45); schlafen D (SEQ ID NO:47); schlafen E (SEQ ID NO:49); and
30 schlafen F (SEQ ID NO:51).

SUMMARY OF THE INVENTION

The present invention is directed to novel genes, e.g., primate embodiments. These genes include receptors related to cytokine receptors, e.g., cytokine receptor like molecular structures, designated DNAX Interferon-like Receptor Subunit 4 (DIRS4); TNF related cytokines designated TNF α and TNF γ ; Toll-like receptor like molecules designated TLR-L1, TLR-L2, TLR-L3, TLR-L4, and TLR-L5; a TGF related molecule designated TGF α ; a soluble Th2 cell produced entity designated 5685C6; a group of genes related to ones whose expression patterns correlate with medical conditions designated claudins, herein referred to as claudins D2, D8, D17, and D7.2; and a second group of genes related to ones whose expression patterns correlate with medical conditions designated schlafens, herein referred to as schlafens B, C, D, E, and F.

In particular, the present invention provides a composition of matter selected from: a substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of: SEQ ID NO: 2 (DIRS4); SEQ ID NO: 9, 11, 13, or 53 (TNF α or TNF γ); SEQ ID NO: 15, 17, 19, 21, 23, 25, or 27 (TLR-L1 through TLR-L5); SEQ ID NO: 29 (TGF α); SEQ ID NO: 31 or 33 (5685C6); SEQ ID NO: 35, 37, 39, or 41 (claudins); SEQ ID NO: 43, 45, 47, 49, or 51 (schlafens). In preferred embodiments, the distinct nonoverlapping segments of identity: include one of at least eight amino acids; include one of at least four amino acids and a second of at least five amino acids; include at least three segments of at least four, five, and six amino acids; or include one of at least twelve amino acids. In certain embodiments, the polypeptide: is unglycosylated; is from a primate, such as a human; comprises at least contiguous seventeen amino acids of the SEQ ID NO; exhibits at least four nonoverlapping segments of at least seven amino acids of the SEQ ID NO; has a length at least about 30 amino acids; has a molecular weight of at least 30 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; or comprises a detection or purification tag, including a FLAG, His6, or Ig sequence. In other embodiments, the composition comprises: a substantially pure polypeptide; a sterile polypeptide; or the polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Kit embodiments include those comprising such a polypeptide, and: a compartment comprising the polypeptide; or instructions for use or disposal of reagents in the kit.

Binding compound embodiments include those comprising an antigen binding site from an antibody, which specifically binds to a described polypeptide, wherein: the binding
5 compound is in a container; the polypeptide is from a human; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised to a recombinant polypeptide; is raised to a purified polypeptide; is immunoselected; is a polyclonal antibody; binds to a denatured antigen; exhibits a K_d to antigen of at least 30 μ M; is attached to a solid substrate, including a bead or plastic
10 membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label.

Kit embodiments include those comprising such a binding compound, and: a compartment comprising the binding compound; or instructions for use or disposal of reagents in the kit.

15 Methods are provided, e.g., for producing an antigen:antibody complex, comprising contacting under appropriate conditions a primate polypeptide with such a described antibody, thereby allowing the complex to form. Also provided are methods of producing an antigen:antibody complex, comprising contacting under appropriate conditions a polypeptide with an antibody which binds thereto, thereby allowing the complex to form. And methods
20 are provided to produce a binding compound comprising: immunizing an immune system with a polypeptide described; introducing a nucleic acid encoding the described polypeptide to a cell under conditions leading to an immune response, thereby producing said binding compound; or selecting for a phage display library for those phage which bind to the desired polypeptide.

25 Further compositions are provided, e.g., comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

30 Nucleic acid embodiments are provided, e.g., an isolated or recombinant nucleic acid encoding a polypeptide described, wherein the: polypeptide is from a primate; or the nucleic acid: encodes an antigenic polypeptide; encodes a plurality of antigenic polypeptide

sequences of SEQ ID NO: 2, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, or 53; exhibits identity over at least thirteen nucleotides to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is a hybridization probe for a gene encoding the polypeptide; or is a PCR primer, PCR product, or mutagenesis primer.

Various embodiments also include cells comprising the recombinant nucleic acids, particularly wherein the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Kit embodiments include those comprising a described nucleic acid, and: a compartment comprising the nucleic acid; a compartment further comprising a primate polypeptide; or instructions for use or disposal of reagents in the kit.

Other nucleic acids are provided which: hybridize under wash conditions of 30 minutes at 37° C and less than 2M salt to the coding portion of SEQ ID NO: 1, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52; or exhibit identity over a stretch of at least about 30 nucleotides to a SEQ ID NO: 1, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, or 52. Preferably, the wash conditions are at 45° C and/or 500 mM salt, or at 55° C and/or 150 mM salt; or the stretch is at least 55 or 75 nucleotides.

Methods are provided, e.g., for making: a duplex nucleic acid comprising contacting: a described nucleic acid with a complementary nucleic acid, under appropriate conditions, thereby resulting in hybridization to form the complex; or a nucleic acid complementary to a described nucleic acid with its complementary nucleic acid, under appropriate conditions, thereby resulting in hybridization to form the complex; or a polypeptide comprising culturing a cell comprising a described nucleic acid under conditions resulting in expression of the nucleic acid.

And methods are provided to: modulate physiology or development of a cell comprising contacting the cell with a polypeptide comprising SEQ ID NO: 9, 11, 13, 29, 31, or 33; modulate physiology or development of a cell comprising contacting the cell with a binding compound which binds to SEQ ID NO: 9, 11, 13, 29, 31, 33 or 53, thereby blocking signaling mediated by a protein comprising the SEQ ID NO; label a cell comprising contacting

the cell with a binding compound which binds to SEQ ID NO: 15, 17, 19, 21, 13, 15, or 37; or diagnose a medical condition comprising a step of evaluating expression of nucleic acid comprising SEQ ID NO: 34, 36, 38, 40, 42, 44, 46, 48, or 50.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. General

The present invention provides the amino acid sequences and nucleic acid sequences of mammalian, herein primate, genes. Among them is an interferon receptor-like subunit molecule, one designated DNAX Interferon Receptor family Subunit 4 (DIRS4), having
10 particular defined properties, both structural and biological. Others include molecules designated TNF α and TNF γ ; Toll like receptor like molecules TLR-L1, TLR-L2, TLR-L3, TLR-L4, and TLR-L5; TGF α ; 5685C6; claudins D2, D8, D17, and D7.2; and schlafens B, C, D, E, and F. Various cDNAs encoding these molecules were obtained from primate, e.g.,
15 human, cDNA sequence libraries. Other primate or other mammalian counterparts would also be desired. In certain cases, alternative splice variants should be available.

Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d
20 ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

A nucleotide and corresponding amino acid sequence for a primate, e.g., human DIRS4
25 coding segment is shown in SEQ ID NO: 1 and 2, respectively. The new DIRS4 lacks a transmembrane segment, which suggests that the subunit acts as a soluble subunit, and would thus be an alpha receptor subunit. Alternatively, or in addition, a splice variant would exist which contains a transmembrane segment. This is consistent with the observation that two transcripts are found in many cell types. Interferon receptor like subunits may be receptors
30 for the IL-10 family of ligands, e.g., IL-10, AK155, IL-19, IL-20/mda-7, AK155, IL-D110, IL-D210, etc. See, e.g., Derwent patent sequence database.

Also provided are nucleotide (SEQ ID NO: 8, 10, 12, and 52) and corresponding amino acid sequences (SEQ ID NO: 9, 11, 13, and 53) for primate and rodent forms of TNF α and primate and rodent forms of TNF γ . Features for primate TNF α include: cAMP PK sites about 38, 74, 79, 205; Cas Phos sites about 41, 61; Cyt $_c$ -Me site about 35; Myristoly sites about 5, 57, 220, 232 N-GLYCOSYL site about 229; PHOS2 sites about 38-41, 79-82, 134-136; PKC ph sites about 77, 142. Also segments 119-250, and 209-221 are notable. For rodent TNF α , features include: A predicted signal 1-19; mature would begin at about 20. Other features: cAMP PK sites at about 34, 93, 132, 229, 248, 263; Cas Phos sites about 119, 232, 251; Cyt $_c$ -Me sites about 26, 90, 172; Histone-Me site about 82; Myristoly sites around 278, 290, 303; N-GLYCOSYL: 3 sites about 39, 287, 297; PHOS2 sites about 26-29, 34-37, 90-92, 93-96, 138-140, 192-194, 248-251; and PKC ph sites about 43, 51, 80, 81, 152; TyKinsite about 154. Signal cleavage site predicted between pos. 19 and 20: AGA-GA. Other significant segments include from about 74-132, 94-118, 168-308, and 193-201.

Nucleotide and corresponding amino acid sequences for TLR-L1 through TLR-L5 are provided in SEQ ID NO:14-27. The EST distribution for TLR1 suggests mRNA expression is restricted to brain tissue; chromosome Xq27.1-28 coding region is on a single exon. Features for primate TLR1 (SEQ ID NO:15) include: Tyr Kin site about 704 (KEGDPVAY); Tyr Kin sites about 713 (RNLQEFSY), 825(KPQSEPDY); N-GLYCOSYL sites about 84 (NYS), 219 (NCT), 294 (NPT), 366 (NIS), 421 (NLT), 583 (NLS); likely a Type Ia membrane protein; a possible uncleavable N-term signal sequence; and a transmembrane prediction of about 618-634 <612-646>. For rodent TLR-L1 (SEQ ID NO:17), the features include: A predicted transmembrane segment from about residues 56-75; and predicted TyKin sites at about residues 136 and 145.

For primate TLR-L2 (SEQ ID NO:19) features include: N-glycosyl sites about 82 (NYT), 217 (NCS), 623 (NST), 674 (NQS); TyKin sites about 889 (RLREPVLY), 450 (RLSPELFY), 917 (KLNVEPDY); TyKin site about 889 (RLREPVLY), 917 (KLNVEPDY). Structurally this molecule has homology to type Ia membrane proteins.

Primate TLR-L3 (SEQ ID NO:23) has the following features: SIGNAL 1-26; TRANS 14-34; Pfam:LRRNT 43-73; Pfam:LRR 78-101; LRR_TYP 100-123; Pfam:LRR 102-125; LRR_TYP 124-147; Pfam:LRR 126-149; LRR_TYP 148-171; Pfam:LRR 150-173;

LRR_TYP 172-195; LRR_PS 172-194; Pfam:LRR 174-197; LRR_TYP 196-219; LRRCT 232-282; Pfam:LRRCT 232-282 with SEG 331-349 or SEG 365-379; Pfam:LRRNT 372-405; LRRNT 372-410; Pfam:LRR 409-432; LRR_TYP 431-454; Pfam:LRR 433-456; LRR_PS 455-477; LRR_TYP 455-478; Pfam:LRR 457-480; LRR_TYP 479-502; Pfam:LRR 481-504
 5 with SEG 502-519; LRR_TYP 503-526; LRR_PS 503-525; Pfam:LRR 505-528; Pfam:LRRCT 562-612; LRRCT 562-612; TRANS 653-673; SEG 653-676; SEG 712-723; SEG 760-776; SEG 831-855. Structurally this molecule has homology to type Ia membrane proteins.

Primate TLR-L4 (SEQ ID NO:25) EST distributions suggest mRNA expression is
 10 restricted to brain tissue; human chromosome Xq26.3-28; predicted features at about, e.g., SIGNAL 1-18; SEG 22-38; Pfam:LRR 60-83; LRR_TYP 82-105; Pfam:LRR 84-107; LRR_PS 106-128; LRR_TYP 106-129; Pfam:LRR 108-131; LRR_TYP 130-153; Pfam:LRR 132-155; LRR_SD22 154-174; LRR_PS 154-176; LRR_TYP 154-177; Pfam:LRR 156-178; LRR_SD22 177-198; LRR_PS 177-198; LRR_TYP 178-201; Pfam:LRR 179-200; Pfam:LRRCT 213-263;
 15 LRRCT 213-263; LRRNT 341-379; Pfam:LRRNT 341-374; Pfam:LRR 378-401; LRR_TYP 400-423; LRR_SD22 400-421; Pfam:LRR 402-425; LRR_TYP 424-447; LRR_SD22 424-450; LRR_PS 424-447; Pfam:LRR 426-449; LRR_TYP 448-471; LRR_PS 448-470; Pfam:LRR 450-473; LRR_TYP 472-495; LRR_PS 472-494; Pfam:LRR 474-497; SEG 474-488; LRRCT 531-581; Pfam:LRRCT 531-581; SEG 617-643; TRANS 623-643; N-
 20 GLYCOSYL sites about 81 (NFS), 216 (NCS), 308 (NPS), 325 (NLS), 423 (NLT); chromosome Xq26.3-28; coding region is on a single exon. Structurally this molecule appears to be a Type Ia membrane protein.

For primate TLR-L5 (SEQ ID NO:27) the entire coding region lies on a single exon on human chromosome 13; predicted features at about, e.g., SIGNAL 1-20; Pfam:LRR 65-88;
 25 LRR_TYP 87-110; Pfam:LRR 89-112; LRR_TYP 111-134; Pfam:LRR 113-136; LRR_PS 135-157; LRR_SD22 135-156; LRR_TYP 135-158; Pfam:LRR 137-160; LRR_TYP 159-182; LRR_SD22 159-177; LRR_PS 159-181; Pfam:LRR 161-184; LRR_SD22 182-203; LRR_TYP 185-206; Pfam:LRR 185-205; LRRCT 218-268; Pfam:LRRCT 218-268; Hybrid:LRRNT 328-364; Pfam:LRRNT 328-360; LRR_SD22 386-407; Pfam:LRR 388-411; LRR_TYP 389-409;
 30 LRR_PS 410-432; LRR_TYP 410-433; LRR_SD22 410-428; Pfam:LRR 412-435; LRR_SD22 434-453; LRR_PS 434-457; LRR_TYP 434-457; Pfam:LRR 436-459; SEG 436-445; LRR_PS

458-480; LRR_SD22 458-484; LRR_TYP 458-481; SEG 459-476; Pfam:LRR 460-483; SEG 503-516; LRRCT 517-567; Pfam:LRRCT 517-567; SEG 585-596; TRANS 607-627; SEG 701-710; N-GLYCOSYL 3 sites about 292 (NDS), 409 (NLT), 572 (NPS); TyKin site about 798 (KLMETLMY).

5 Nucleotide and corresponding amino acid sequences for a primate, e.g., human, TGF α coding segment, are represented by SEQ ID NO:28 and 29, respectively. Human TGF α maps to chromosome 5 (clone CITB-H1_2319M24). Predicted features (SEQ ID NO: 29) include: TGFB domain 115-212; Pfam:TGF-beta 115-167; Pfam:TGF-beta 205-212; TGF-beta like conserved Cys residues at positions 115, 144, 148, 177, 209, 211.

10 Nucleotide and corresponding amino acid sequences for 5685C6 coding segments are presented in SEQ ID NO:30-33. The primate clone maps to chromosome 21q22.1. Features of primate 5685C6 (SEQ ID NO:31) include: N-GLYCOSYL sites about 10 (NST), 23 (NCS), 76 (NFT), 169 (NVT), 191 (NKS); most likely cleavage site predicted between pos. 19 and 20: VFA-LN. The secreted protein produced by Th2 cells. The corresponding rodent polypeptide (SEQ ID NO:33) has the following features Predicted features: N-GLYCOSYL
15 sites about 6 (NNT), 19 (NCS), 159 (NRS); most likely cleavage site between pos. 26 and 27: TKA-QN. 5685C6 molecules appear to be soluble entities which are expressed in Th2 clones. The entities are useful markers of Th2 cells, and will be useful in characterizing such cell types.

20 Nucleotide and corresponding amino acid sequences for claudins D2, D8, D17, and D7.2 are SEQ ID NO:34-41 (See, e.g., Simon, et al. (1999) Science 285:103-106).

Nucleotide and corresponding amino acid sequences for schlafens B, C, D, E, and F (see, e.g., see Schwarz, et al. (1998) Immunity 9:657-668) are SEQ ID NO:42-51.

As used herein, the term DIRS4 shall be used to describe a protein comprising a
25 protein or peptide segment having or sharing the amino acid sequence shown in the SEQ ID NOs noted above, or a substantial fragment thereof. The invention also includes a protein variation of the respective DIRS4 allele whose sequence is provided, e.g., a mutein or soluble extracellular construct. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1- and 11-fold substitutions, e.g.,
30 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological

ligand, perhaps in a dimerized state with a second receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein.

Likewise, reference to the other genes described herein will be made. General descriptions directed to the methods of making or structural features will often be applicable to the other entities provided herein, e.g., the TNF α , TNF γ , TLR-L1, TLR-L2, TLR-L3, TLR-L4, TLR-L5, TGF α , 5685C6, claudins D2, D8, D17, D7.2, and schlafens B, C, D, E, and F. Antibodies thereto, nucleic acids encoding them, etc., will be similarly applicable to the different entities.

This invention also encompasses proteins or peptides having substantial amino acid sequence identity with the amino acid sequences. It will include sequence variants with relatively few substitutions, e.g., preferably less than about 3-5.

A substantial polypeptide "fragment", or "segment", is a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Sequences of segments of different proteins can be compared to one another over appropriate length stretches.

Fragments may have ends which begin and/or end at virtually all positions, e.g., beginning at residues 1, 2, 3, etc., and ending at, e.g., the carboxy-terminus (N), N-1, N-2, etc., in all practical combinations of different lengths. Particularly interesting polypeptides have one or both ends corresponding to structural domain or motif boundaries, as described, or of the designated lengths with one end adjacent one of the described boundaries. In nucleic acid embodiments, often segments which encode such polypeptides would be of particular interest.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches. In some comparisons, gaps may be introduced, as required. See, e.g.,

Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This analysis is especially important when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if conservative substitutions are included) with an amino acid sequence segment of the appropriate SEQ ID NOs noted above. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described individually, e.g., in the various tables.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by cytokine-like ligands. For example, the receptors typically should mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates.

The terms ligand, agonist, antagonist, and analog of, e.g., a DIRS4_ include molecules that modulate the characteristic cellular responses to cytokine ligand proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural receptor or an antibody. The cellular responses likely are typically mediated through receptor tyrosine kinase pathways.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. See, e.g., Herz, et al. (1997) J. Recept. Signal Transduct. Res. 17:671-776; and Chaiken, et al. (1996) Trends Biotechnol. 14:369-375. Effectors may be other proteins which mediate other functions in response to ligand binding, or other proteins which normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

II. Activities

The cytokine receptor-like proteins will have a number of different biological activities, e.g., modulating cell proliferation, or in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other innate immunity response, or a morphological effect. The subunit will probably have a specific low affinity binding to the ligand.

Different receptors may mediate different signals. The TLR-L receptors may signal similar biology to the TLRs, which mediate fundamental innate immune or developmental responses. See, e.g., Aderem and Ulevitch (2000) Nature 406:782-787. The TNFs and TGF are likely to signal as cytokines, as may the 5685C6, which seemingly is expressed by Th2 cells. The 5685C6 genes appear to be secreted proteins, which exhibit a cleavable signal sequence.

The claudins appear to be membrane proteins exhibiting 4 transmembrane segments, and seem to be associated with tight junctions and/or paracellular transport. They may also affect epithelial permeability or conductances, e.g., ion, across membranes. The claudin-D2 member of the claudin family is found to have regulated expression correlating with Crohn's disease. The other family members exhibit differential regulation in disease states, e.g., in Crohn's disease, ulcerative colitis, and various interstitial lung diseases. This is consistent with an important role in these disease processes. A functional role in the tight junctions/paracellular transport is consistent with problems in intestinal physiology.

Claudins define a structurally related multi-gene family of 4 TM proteins with distinct tissue distribution patterns. The claudins are major structural proteins of tight junctions (TJs) and can promote their formation. Their expression is necessary but not sufficient for tight junction formation. When expressed in fibroblasts, claudin-1 is capable of inducing a continuous association of adjacent cells, resulting in a cobblestone like pattern. However, this continuous barrier is not a tight junction. Claudins can be found outside of tight junction in certain cells. Claudin-3 and claudin-4 are receptors for Clostridium perfringens enterotoxin, a causative agent of fluid accumulation in the intestinal tract, causing diarrhea. Claudin-5 is deleted in Velo-cardio-facial syndrome (VCFS). Claudin-5 is only expressed in endothelial cells, and in some tissues it is even further restricted to arterials.

Mutations in Paracellin-1, claudin family member and a major renal tight junction protein, cause renal magnesium wasting with nephrocalcinosis. Thus, claudins may play important roles in selective paracellular conductance by determining the permeability of different epithelia.

The schlafens are members of a family of proteins of whose members are growth regulatory genes. See, e.g., Schwarz, et al. (1998) Immunity 9:657-668. These novel human sequences are related to the mouse Schlafen2 gene. It was observed to be differentially

regulated in mouse IBD: Rag Hh+ (IL-10 treated) colon expression was higher than Rag Hh+ alone and mimicked the expression of Rag Hh-.

The DIRS4 has the characteristic extracellular motifs of a receptor signaling through the JAK pathway. See, e.g., Ihle, et al. (1997) Stem Cells 15(suppl. 1):105-111; Silvennoinen, et al. (1997) APMIS 105:497-509; Levy (1997) Cytokine Growth Factor Review 8:81-90; Winston and Hunter (1996) Current Biol. 6:668-671; Barrett (1996) Baillieres Clin. Gastroenterol. 10:1-15; and Briscoe, et al. (1996) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351:167-171.

The biological activities of the cytokine or other receptor subunits will be related to addition or removal of phosphate moieties to substrates, typically in a specific manner, but occasionally in a non specific manner. Substrates may be identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

III. Nucleic Acids

This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers isolated or recombinant DNAs which encode such proteins or polypeptides having characteristic sequences of the DIRS4 or the other genes. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence segment shown in the appropriate SEQ ID NOs noted above, but preferably not with other genes. Said biologically active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous, e.g., exhibiting significant stretches of identity, to ones described. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are equivalent to the described proteins. The isolated nucleic acids can have

the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which naturally
5 accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.
10 A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or
15 activity.

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although
20 under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, for example, products made by transforming cells with an unnaturally occurring vector is encompassed, as
25 are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired
30 combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target of such artificial

manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic
5 code redundancy, encode equivalent polypeptides to fragments of the described sequences and fusions of sequences from various different related molecules, e.g., other cytokine receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least 21 nucleotides, more generally at least 25 nucleotides, ordinarily
10 at least 30 nucleotides, more ordinarily at least 35 nucleotides, often at least 39 nucleotides, more often at least 45 nucleotides, typically at least 50 nucleotides, more typically at least 55 nucleotides, usually at least 60 nucleotides, more usually at least 66 nucleotides, preferably at least 72 nucleotides, more preferably at least 79 nucleotides, and in particularly preferred embodiments will be at least 85 or more nucleotides. Typically, fragments of different genetic
15 sequences can be compared to one another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for, e.g., a DIRS4, will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different
20 individuals or related species. Other genes will be useful as markers for particular cell types, or diagnostic of various physiological conditions. Preferred probes for such screens may, in certain circumstances, be those regions of the gene which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations, polymorphic variant specific sequences will be
25 more useful.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. Alternatively, recombinant clones derived
30 from the genomic sequences, e.g., containing introns, will be useful for transgenic studies, including, e.g., transgenic cells and organisms, and for gene therapy. See, e.g., Goodnow

(1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; Robertson (1987)(ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199. Operable association of heterologous promoters with natural gene sequences is also provided, as are vectors encoding, e.g., the DIRS4 with a receptor partner. See, e.g., Treco, et al. WO96/29411 or USSN 08/406,030.

Homologous, or highly identical, nucleic acid sequences, when compared to one another, e.g., DIRS4 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a described sequence. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nucl. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more

nucleotides. This includes, e.g., 125, 150, 175, 200, 225, 250, 275, 300, 400, 500, 700, 900, and other lengths.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30° C, more usually in excess of about 37° C, typically in excess of about 45° C, more typically in excess of about 55° C, preferably in excess of about 65° C, and more preferably in excess of about 70° C. Stringent salt conditions will ordinarily be less than about 500 mM, usually less than about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant derivatives include predetermined or site-specific mutations of the protein or its fragments, including silent mutations using genetic code degeneracy. "Mutant DIRS4" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DIRS4 as set forth above, but having an amino acid sequence which differs from that of other cytokine receptor-like proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DIRS4" encompasses a protein having substantial sequence identity with a protein of SEQ ID NO:2, and typically shares most of the biological activities or effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DIRS4 mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many

combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy- terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DIRS4 mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

Antisense and other technologies for blocking expression of these genes are also available. See, e.g., Misquitta and Paterson (1999) Proc. Nat'l Acad. Sci. USA 96:1451-1456.

IV. Proteins, Peptides

As described above, the present invention encompasses primate DIRS4, e.g., whose sequences are disclosed in SEQ ID NO:2, and described above. Allelic and other variants are also contemplated, including, e.g., fusion proteins combining portions of such sequences with others, including epitope tags and functional domains. Analogous methods and applications exist directed to the other genes described herein.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of

proteins or segments which are naturally not normally fused in the same manner. Thus, e.g., the fusion product of a DIRS4 with another cytokine receptor is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., cytokine receptors or Toll-like receptor like genes, including species variants. For example, ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992, each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference.

The present invention particularly provides muteins which bind cytokine-like ligands, and/or which are affected in signal transduction. Structural alignment of human DIRS4 with other members of the cytokine receptor family show conserved features/residues. Alignment of the human DIRS4 sequence with other members of the cytokine receptor family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269. Similarly, the other genes have related family members.

Substitutions with either mouse sequences or human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction

regions will probably preserve most signaling activities; and conservative substitutions away from the intracellular domains will probably preserve most ligand binding properties.

"Derivatives" of the various proteins include amino acid sequence mutants, glycosylation variants, metabolic derivatives, and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties, including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the proteins or fragments thereof with other proteins or polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the proteins and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different proteins, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different cytokine ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a

combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated
5 herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial β -galactosidase, trpE, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded
10 fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other
15 moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression
20 are described generally, for example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-
25 2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of these proteins other than
30 variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three

classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a cytokine ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of an cytokine receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A polypeptide of this invention can be used as an immunogen for the production of antisera or antibodies. These may be specific, e.g., capable of detecting or distinguishing between other related family members or various fragments thereof. The purified proteins can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. The purified proteins can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, fragments may also serve as immunogens to produce the antibodies of the present invention. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino acid sequences provided, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surfaces.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Antibodies to ligands may be antagonists. Thus, in vitro assays of the present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to

solid phase substrates. Assays will also allow for the diagnostic determination of the effects of mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to the receptor or fragments compete with a test compound for
5 binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

10 V. Making Nucleic Acids and Protein

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein. Other species counterparts can be identified by
15 hybridization techniques, or by various PCR techniques, or combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host cells which can, in turn, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified constructs; and for structure/function studies. Variants or fragments
20 can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other
25 proteins.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to
30 effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression

control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a protein, as described, or a fragment thereof encoding a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNA coding for such a protein in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the receptor is inserted into the vector such that growth of the host containing the vector expresses the cDNA in question. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the protein encoding portion or its fragments into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds. 1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Butterworth, Boston, which are incorporated herein by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with receptor vectors constructed using recombinant DNA techniques.

Transformed host cells usually express the desired protein or its fragments, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the subject protein. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the receptor to accumulate in the cell membrane. The protein can be recovered,
5 either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is
10 operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

15 Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian
20 origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments
25 include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their Uses, (eds. Rodriguez and Denhardt), Butterworth,
30 Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with DIRS4 sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available.

5 Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol
10 dehydrogenase 2 promoter or metallothioneine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YE_p-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YC_p-series).

Higher eukaryotic tissue culture cells are normally the preferred host cells for
15 expression of the functionally active interleukin protein. In principle, many higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby
20 rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses
25 carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

30 For secreted proteins, an open reading frame usually encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal

peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690 and Nielsen, et al. (1997) Protein Eng. 10:1-12, and the precise amino acid composition of the signal peptide often does not
5 appear to be critical to its function, e.g., Randall, et al. (1989) Science 243:1156-1159; Kaiser et al. (1987) Science 235:312-317.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the
10 polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells.

The source of protein can be a eukaryotic or prokaryotic host expressing recombinant
15 gene, such as is described above. The source can also be a cell line such as mouse Swiss 3T3 fibroblasts, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, the primate protein, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include
20 processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process,
25 a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial polypeptide sequences.

30 The various proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a

so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

5 If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated
10 resins, and the like.

 An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase
15 approach is generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

 The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, e.g., by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The proteins of this
20 invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked
25 antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells producing the protein as a result of DNA techniques, see below.

 Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more
30 typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually

be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate.

VI. Antibodies

5 Antibodies can be raised to the various mammalian, e.g., primate DIRS4, proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which
10 would be useful as agonists or antagonists of a natural receptor or an antibody.

 Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to
15 normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μ M, typically at least about 100 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better.

 The antibodies, including antigen binding fragments, of this invention can have
20 significant diagnostic or therapeutic value. They can be potent agonists or antagonists, e.g., that bind to the receptor and inhibit or simulate binding to ligand, or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies or for use as markers for detection or diagnosis, and can be coupled to toxins or radionuclides to bind producing cells. Further, these antibodies can be
25 conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

 The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the antigen without inhibiting, e.g., ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive
30 binding assays. They will also be useful in detecting or quantifying antigen. They may be

used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian cytokine receptors, cytokines, enzymes, marker proteins, and fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera. A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin

Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156.

The antibodies of this invention can also be used for affinity chromatography in isolating the proteins or peptides. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. Conversely, the protein may be used to purify antibody by immunoselection.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies raised against a protein will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of a ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A target protein that specifically binds to or that is specifically immunoreactive with an antibody generated against it, such as an immunogen consisting of a described amino acid sequence, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 2. This antiserum is selected to have low crossreactivity against other cytokine receptor family members, e.g., IFN

receptor subunits, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 2, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, *supra*). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other cytokine receptor family members, e.g., receptors aligned in Figure 1, using a competitive binding immunoassay such as the one described in Harlow and Lane, *supra*, at pages 570-573. Preferably at least two cytokine receptor family members are used in this determination. These cytokine receptor family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 2 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to selected other receptor subunits. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein. In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein

required is less than twice the amount of the protein of the selected protein or proteins that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that these proteins are members of families of homologous proteins.

5 For a particular gene product, such as the DIRS4, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-allelic, or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new

10 amino acids, or adding new amino acids. Such minor alterations typically will substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring DIRS4 protein. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate

15 effect, e.g., upon transfected lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the cytokine receptor family as a whole. By aligning a protein optimally with the protein of the cytokine receptors and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of

20 the invention.

VII. Kits and quantitation

Both naturally occurring and recombinant forms of the molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be

25 applied to screening for binding activity, e.g., ligands or receptors for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773, which is incorporated herein by reference. The latter describes means for testing binding by a

30 plurality of defined polymers synthesized on a solid substrate. The development of suitable assays to screen for a ligand or agonist/antagonist homologous proteins can be greatly

facilitated by the availability of large amounts of purified, soluble cytokine receptors in an active state such as is provided by this invention. Alternatively, production of large amounts of ligand will be useful in screening for receptor. Markers will also be available in large amounts to generate specific reagents.

5 Purified protein, e.g., DIRS4, can be coated directly onto plates or otherwise presented for use in the ligand or antibody screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of, e.g., DIRS4, fragments thereof, peptides, and
10 their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its ligand. Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing either a peptide or gene segment or a reagent which recognizes one or the other. Typically, recognition reagents, in the case of peptide, would be a receptor or antibody, or in
15 the case of a gene segment, would usually be a hybridization probe. Diagnostic applications will be useful for the markers, as described.

A preferred kit for determining the concentration of, e.g., DIRS4, in a sample would typically comprise a labeled compound, e.g., ligand or antibody, having known binding affinity for DIRS4, a source of DIRS4 (naturally occurring or recombinant) as a positive
20 control, and a means for separating the bound from free labeled compound, for example a solid phase for immobilizing the DIRS4 in the test sample. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, specific for mammalian claudins or
25 schlafens or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of protein and/or its fragments. Diagnostic assays may be homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme
immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled
30 fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a

cytokine receptor or to a particular fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (ed. 1991 and periodic supplements) Current Protocols In Immunology Greene/Wiley, New York.

5 Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of cytokine receptors or ligands. These should be useful as therapeutic reagents under appropriate circumstances.

 Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the
10 assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain
15 instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium having appropriate concentrations for performing the assay.

 The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved
20 by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, a test compound, cytokine receptor, ligand, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable
25 of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

 There are also numerous methods of separating the bound from the free ligand, or
30 alternatively the bound from the free test compound. The cytokine receptor can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such

as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen complex by any of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

Methods for linking protein or fragments to various labels are well reported in the literature. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequences provided. These sequences can be used as probes for detecting levels of the respective genes or transcripts in patients suspected of having an immunological or other medical disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly ^{32}P . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex

can be detected. The use of probes to the novel anti-sense RNA may be carried out in conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

VIII. Therapeutic Utility

This invention provides reagents with significant therapeutic value. See, e.g., Levitzki (1996) Curr. Opin. Cell Biol. 8:239-244. The cytokine receptors (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should be useful in the treatment of conditions exhibiting abnormal expression of the receptors or their ligands. Such abnormality will typically be manifested by immunological or other disorders. Additionally, this invention should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering of response to the ligand. The biology of interferons, IL-10, TNFs, and TGFs are well described. Conversely, the TLRs have also been the subject of much interest, and the described homologs described herein will also be of similar interest. Associations with significant medical conditions for the claudins and schlafens is described below.

Recombinant proteins, muteins, agonist or antagonist antibodies thereto, or antibodies can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof which are not complement binding.

Ligand screening using receptor or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to cytokine receptors as antagonists.

Conversely, receptor screening for receptors for ligands can be performed. However, ligands can also be screened for function using biological assays, which are typically simple due to the soluble nature of the ligands.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, reagent physiological life, pharmacological life, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

Cytokines, receptors, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, e.g., agonists or antagonists of other cytokine receptor family members.

IX. Screening

Drug screening using DIRS4, TLR-L receptors, or fragments thereof can be performed to identify compounds having binding affinity to the receptor subunits, including isolation of associated components. See, e.g., Emory and Schlegel (1996) Cost-Effective Strategies for Automated and Accelerated High-Throughput Screening IBC, Inc., Southborough, MA. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of a cytokine ligand. This invention

further contemplates the therapeutic use of antibodies to the receptor as cytokine agonists or antagonists.

Conversely, for ligands, receptors may be screened. Orphan receptor subunits, or testing of known receptor subunits in known or novel pairings may be performed.

5 One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing the DIRS4 or TLR-L receptors. Cells may be isolated which express a receptor in isolation from other functional receptors, or in combination with other specific subunits. Such cells, either in viable or fixed form, can be used for standard ligand/receptor binding assays. See also, Parce, et al. (1989)
10 Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of putative ligand) are contacted and incubated with a labeled receptor or antibody having known binding affinity to the ligand, such as ^{125}I -
15 antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of ligand binding. The amount of test compound bound is inversely proportional to the amount of labeled receptor binding to the known source. Any one of numerous techniques can be used to separate bound from free ligand to assess the degree of ligand binding. This separation step could typically involve a procedure such as adhesion to filters followed by
20 washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on cytokine mediated functions, e.g., second messenger levels, i.e., Ca^{++} ; cell proliferation; inositol phosphate pool changes; and others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system. Calcium sensitive dyes will be useful for detecting
25 Ca^{++} levels, with a fluorimeter or a fluorescence cell sorting apparatus.

X. Ligands

The descriptions of the DIRS4 and TLR-L receptors herein provide means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor
30 with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to detect its ligand. For example, directly labeling cytokine receptor,

fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available
5 cytokine receptor sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

Generally, descriptions of cytokine receptors will be analogously applicable to individual specific embodiments directed to DIRS4 or TLR-L reagents and compositions. Conversely, soluble ligands, e.g., TNFs and TGFs, will be characterized for biological activity.

The broad scope of this invention is best understood with reference to the following
10 examples, which are not intended to limit the inventions to the specific embodiments.

EXAMPLES

I. General Methods

15 Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning. A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular
20 Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in Methods in
25 Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of
30 Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering,

Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence
5 databases were also used, e.g., from GenBank and others.

Many techniques applicable to IL-10 or IL-12 receptors may be applied to the DIRS4 or other receptor subunits, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference.

10 II. Computational Analysis

Human sequences were identified from genomic sequence database using, e.g., the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). Standard analysis programs may be used to evaluate structure, e.g., PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310). Standard comparison software
15 includes, e.g., Altschul, et al. (1990) J. Mol. Biol. 215:403-10; Waterman (1995) Introduction to Computational Biology: Maps, Sequences, and Genomes Chapman & Hall; Lander and Waterman (eds. 1995) Calculating the Secrets of Life: Applications of the Mathematical Sciences in Molecular Biology National Academy Press; and Speed and Waterman (eds. 1996) Genetic Mapping and DNA Sequencing (Ima Volumes in Mathematics and Its Applications,
20 Vol 81) Springer Verlag.

III. Cloning of full-length cDNAs; Chromosomal localization

PCR primers derived from the sequences are used to probe a human cDNA library. Full length cDNAs for primate, rodent, or other species DIRS4 are cloned, e.g., by DNA
25 hybridization screening of λ gt10 phage. PCR reactions are conducted using T. aquaticus Taqplus DNA polymerase (Stratagene) under appropriate conditions.

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine was added for the final seven hours of culture (60
30 μ g/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is labeled by nick-translation with ^3H . The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of hybridization solution as described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

5 After coating with nuclear track emulsion (KODAK NTB₂), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis. Alternatively, mapped sequence tags may be searched in a
10 database.

Similar appropriate methods are used for other species.

IV. Localization of mRNA

Human multiple tissue (Cat # 1, 2) and cancer cell line blots (Cat # 7757-1), containing
15 approximately 2 μg of poly(A)⁺ RNA per lane, are purchased from Clontech (Palo Alto, CA). Probes are radiolabeled with [α - ^{32}P] dATP, e.g., using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and hybridizations are performed at 65° C in 0.5 M Na₂HPO₄, 7% SDS, 0.5 M EDTA (pH 8.0). High stringency washes are conducted, e.g., at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by
20 a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes are then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southern are performed with selected human DIRS4 clones to examine their expression in hemopoietic or other cell subsets.

Alternatively, two appropriate primers are selected, e.g., from the tables. RT-PCR is
25 used on an appropriate mRNA sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Full length clones may be isolated by hybridization of cDNA libraries from appropriate tissues pre-selected by PCR signal. Northern blots can be performed.

Message for genes encoding each gene will be assayed by appropriate technology, e.g.,
30 PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are

available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a physiological responsiveness to each of the cytokine ligands.

5 For mouse distribution, e.g., Southern Analysis can be performed: DNA (5 µg) from a primary amplified cDNA library was digested with appropriate restriction enzymes to release the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for mouse mRNA isolation may include: resting mouse fibroblastic L cell line
10 (C200); Braf:ER (Braf fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN-γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN-γ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T
15 cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 µg/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last stimulation with antigen (T207); TH2 T cell clone
20 CDC35, 10 µg/ml ConA stimulated 15 h (T208); Mel14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN-γ/IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel14+ T cells, polarized to Th2 with IL-4/anti-IFN-γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS
25 activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled (M204);
30 aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206);

Nippostrongylus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202);
 5 total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue
 10 (O300); and rat arthritic joint tissue (X300).

Samples for human mRNA isolation may include: peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3
 15 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for
 20 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN- γ , TH2 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random $\gamma\delta$ T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell
 25 EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with
 30 PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101);

elutriated monocytes, activated with LPS, IFN γ , anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFN γ , IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFN γ , anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with LPS, IFN γ , IL-10 for 4, 16 h pooled (M107);

5 elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNF α 12 days

10 FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC

15 from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNF α , monocyte supe for 4, 16 h pooled (D110); leiomyoma L11 benign tumor (X101); normal myometrium M5 (O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with

20 PMA and ionomycin for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta

25 28 wk (O113); and tonsil inflamed, from 12 year old (X100).

For the DIRS4, southern blot analysis revealed expression in several cDNA libraries, including resting MOT72 (Th0 clone); resting, activated, and anti-peptide HY06 (Th1 clone); activated T cells CD4+, Th2 polarized; resting pooled T cell clones; resting and activated splenocytes; resting EBV B cells; activated JY (B cell line); cytotoxic NK cells; TF1 cells;

30 resting and activated U937 cells; monocytes treated with anti-IL-10; monocytes (anti-IL-10 and IL-10 stimulated); activated monocytes; dendritic cells (activated and resting); MRC5

(lung fibroblast sarcoma line); CHA (kidney epithelial carcinoma line); normal and asthmatic monkey lung; normal and smoker lung; normal colon; fetal lung; liver; gall bladder; and small intestine. There were two transcript sizes, about 500 bp and about 1.8 kb bands, suggesting two different transcripts, possibly soluble and membrane spanning forms.

- 5 The primate, e.g., human, TNF α expression, by PCR, is high in allergic lung and normal lung; much lower in adult placenta, fetal spleen, and normal skin. Essentially no expression in gut samples and fetal organs. In cells, high expression was detected in resting HY06 cells and TF-1; lower in activated HY06 cell and JY cells, and no significant expression in the other human samples tested, e.g., most in the list above. Table 1 shows additional TaqMan
- 10 expression data for human TNF α .

Table 1:

LIBRARY	Ct_gene	LIBRARY	Ct_gene
PBMC resting	44.64 mono + anti-IL-10		22.47
PBMC activated	40.48 mono + IL-10		21.04
Mot 72 resting	26.29 M1		40.52
Mot 72 activated	24.51 M6		21.75
Mot 72 anti-peptide	20.72 70% DC resting		26.27
HY06 resting	15.86 D1		37.94
HY06 activated	18.3 D6		25.05
HY06 anti-peptide	24.27 CD1a+ 95%		26.87
HY935 resting	25.97 CD14+ 95%		35.17
HY935 activated	25.03 CD1a+ CD86+		27.48
B21 resting	26.3 DC/GM/IL-4		32.33
B21 activated	24.53 DC LPS		27.81
Tc gamma delta	45 DC mix		27.32
Jurkat resting pSPORT	45 fetal kidney		26.41
Jurkat activated pSPORT	28.09 fetal lung		31.16
Splenocytes resting	23.51 fetal liver		26.28
Splenocytes activated	26.19 fetal heart		34.28
Bc	23.88 fetal brain		25.02
JY	19.29 fetal small intestine		37.89
NK pool	38.21 fetal adipose tissue		26.41
NK pool activated	37.54 fetal ovary		37.49
NKA6 pSPORT	34.39 fetal uterus		26.03
NKL/IL-2	25.71 fetal testes		36.65
NK cytotox.	23.28 fetal spleen		23.2
NK non cytotox.	26.35 adult placenta		24.06
U937/CD004 resting	28.18 inflamed tonsil		26.21
U937 activated	26.21 TF1		23.48
C-	27 MRC5		33.99

LIBRARY	Ct_gene	LIBRARY	Ct_gene
C+	23.13	CHA	28.27
mast cell pME	28.65	Taq_control_genomic_2	50
TC1080 CD28- pMET7	38.1	Crohns colon 403242A	28.32
RV-C30 TR1 pMET7	24.97	lung 080698-2	27.42
DC resting mono-derived	28.12	18 hr. Ascaris lung	28.06
DC CD40L activ. mono-deriv.	27.07	hi dose IL-4 lung	34.01
DC resting CD34-derived	28.9	normal colon #22	44.6
DC TNF/TGFb act CD34-der.	36.74	ulcerative colitis colon #26	38.12
allergic lung #19	20.21	normal thyroid	28.14
Pneumocystis carinii lung #20	36.33	Hashimotos thyroiditis	36.88
RA synovium pool	28	normal skin	24.12
Psoriasis skin	32.37	Crohns colon 4003197A	30.31
normal lung	35.68	lung 121897-1	36.25
4 hr. Ascaris lung	31.45	Crohns colon 9609C144	27.49
24 hr. Ascaris lung	26.34	A549 unstim.	28.03
normal lung pool	22.21	A549 activated	24.1
Taq_control_genomic_1	50	Taq_control_water	50

- The rodent, e.g., mouse, TNF α is highly expressed in 5 month ApoE KO mouse aorta; C57B6 3 wk polarized Th1 cells; and C57B6 3 wk polarized Th2 cells. It is less highly expressed in Balb/c 3 wk polarized Th2 cells, LPS treated spleen, and various other Th2 polarized populations. In tissues, by PCR, it is expressed highly in TNK KO spleen, NZB/W spleen, NZB/W kidney, NZB/W spleen, GF ears/skin; rag-1 testis, w.t. C57B6 spleen, w.t. C57B6 pancreas, and 2 mo. lung. It is expressed at lower levels in influenza lung, rag-1 lung, rag-1 spleen, spinal cord samples, lung samples, stomach, and lymph nodes. Table 2 shows additional TaqMan expression data for mouse TNF α .

Table 2:

LIBRARY	Ct_gene	LIBRARY	Ct_gene
L cell	26 rag-1 brain		24.47
TH1 7 day	26.63 rag-1 testes		38.4
TH2 7 day	24.56 rag-1 lung		22.81
TH1 3 week Balb/C	39.09 rag-1 liver		36.69
TH2 3 week Balb/C	24.48 rag-1 spleen		24.23
preT	36.92 rag-1 thymus		23.91
D1.1 resting	32.74 rag-1 kidney		22.32
D1.1 con A stim.	37.76 w.t. Peyers patches		25.48
CDC35 resting	30.8 w.t. mesenteric lymph nodes		25.59
CDC35 con A stim.	41.92 w.t. colon		28.7
Mel 14+ naive T	28.16 Braf:ER (-) oligo dT		38.53
Mel14+ TH1	29.2 TH1 3 week C57 Bl/6		23.12
Mel 14+ TH2	25.02 TH2 3 week C57 Bl/6		22.54
A20	37.61 TH1 3 week Balb/C fresh		28.02
CH12	25.29 TH2 3 week Balb/C fresh		37.73
lg. B cell	30.34 b.m. DC (YJL) resting		27.99
LPS spleen	24.04 b.m. DC (YJL) aCD40 stim.		40.47
macrophage	28.6 b.m. mf + LPS + aIL-10R		29.74
J774 resting	39.73 b.m. mf + LPS + IL-10		27.67
J774 +LPS + anti-IL-10	36.51 peritoneal mf		37.02
J774 +LPS + IL-10	40.53 MC-9/MCP-12 pMET7		39.68
Nippo-infected lung	25.87 EC		40.13
IL-10 K.O. spleen	24.18 EC + TNFa		40.54
IL-10 K.O. colon	36.97 bEnd3 + TNFa		41.26
asthmatic lung	26.61 bEnd3 + TNFa + IL-10		38.35
w.t. lung	24.06 ApoE aorta 5 month		21.03
w.t. spleen	28.87 ApoE aorta 12 month		34.28
rag-1 heart	26.48 NZ B/W kidney		21.02

LIBRARY	Ct_gene	LIBRARY	Ct_gene
Nippo IL-4 K.O. lung	28.59	NZ B/W spleen	21.2
Nippo anti IL-5 lung	25.73	tolerized & challenged lung	27.17
Influenza lung	23.93	Aspergillus lung	23.32
b common lung 2 month	24.53	Taq_control_water	50
IL-10 K.O. stomach	29.87	Taq_control_genomic_1	50
IL-10 K.O. MLN aIL-12	26.58	Taq_control_genomic_2	50
IL-10 K.O. MLN +IL-10	25.89	w.t. d17 spinal cord EAE model	22.87
Rag-2 Hh- colon	29.2	TNF K.O. d17 spinal cord EAE model	22.84
Rag-2 Hh+ colon	27.1	TNF K.O. spinal cord	23.27
IL-7 K.O./Rag-2 Hh- colon	40	TNF K.O. spleen	20.78
IL-7 K.O./Rag-2 Hh+ colon	40	G.F. ears (skin)	20.7
transfer model IBD	28.1	w.t. spinal cord	22.74
w.t. C57 Bl/6 aorta	39.38	w.t. C57 Bl/6 spleen	22.15
w.t. thymus	27.05	w.t. C57 Bl/6 pancreas	24.75
w.t. stomach	26.49	MM2/MM3 activated. pME	37.67
MM2/MM3 resting pME	37.62		

5 The primate, e.g., human, TNF α is expressed in fetal adipose tissue and fetal ovary. It is expressed at a lower level in fetal brain, Hashimoto's thyroiditis, RA synovium pool, adult placenta, and fetal uterus. It is expressed at lower levels in fetal kidney, normal thyroid, and detectable in Crohn's colon, psoriasis skin, and fetal lung. It is essentially undetectable in other organs evaluated, including various *Ascaris* challenged lung samples. In cell libraries, it is expressed in TF-1 cells, and much lower in CHA cells, and was not significantly expressed in other cell lines tested. Table 3 provides additional TaqMan expression data for human TNF α .

Table 3:

LIBRARY	Ct_gene	LIBRARY	Ct_gene
PBMC resting	45 mono + IL-10		42.96
PBMC activated	44.16 M1		41.25
Mot 72 resting	42.47 M6		45
Mot 72 activated	28.59 70% DC resting		40.37
Mot 72 anti-peptide	42.47 D1		28.94
HY06 resting	43.19 D6		28.38
HY06 activated	41.48 CD1a+ 95%		25.63
HY06 anti-peptide	43.28 CD14+ 95%		28.36
HY935 resting	45 CD1a+ CD86+		28.67
HY935 activated	43.62 DC/GM/IL-4		45
B21 resting	41.73 DC LPS		38.8
B21 activated	44.35 DC mix		26.53
Tc gamma delta	43.21 fetal kidney		27.98
Jurkat resting pSPORT	23.44 fetal lung		30.57
Jurkat activated pSPORT	25.19 fetal liver		43.92
Splenocytes resting	38.72 fetal heart		40.84
Splenocytes activated	44.09 fetal brain		26.02
Bc	44.83 fetal small intestine		40.05
JY	43.05 fetal adipose tissue		23.63
NK pool	39.09 fetal ovary		25.85
NK pool activated	44.32 fetal uterus		27.57
NKA6 pSPORT	42.8 fetal testes		45
NKL/IL-2	45 fetal spleen		39.08
NK cytotox.	44.79 adult placenta		28.05
NK non cytotox.	45 inflammed tonsil		45
U937/CD004 resting	24.17 TF1		22.09
U937 activated	24.41 MRC5		26.18
C-	40.38 CHA		19.22
C+	41.17 mast cell pME		43.93

LIBRARY	Ct_gene	LIBRARY	Ct_gene
mono + anti-IL-10	45 TC1080 CD28- pMET7		41.62
DC resting mono-derived	45 RV-C30 TR1 pMET7		42.76
DC CD40L activ. mono-deriv.	45 4 hr. Ascaris lung		45
DC resting CD34-derived	45 24 hr. Ascaris lung		45
DC TNF/TGFb act CD34-der.	39.71 normal lung pool		45
allergic lung #19	43.22 normal skin		42.69
Pneumocystis carinii lung #20	43.81 Crohns colon 4003197A		29.82
normal colon #22	43.66 lung 121897-1		45
ulcerative colitis colon #26	45 Crohns colon 9609C144		41.86
normal thyroid	27.71 A549 unstim.		27.09
Hashimotos thyroiditis	27.4 A549 activated		29.01
RA synovium pool	28 Taq_control_water		50
Psoriasis skin	31.49 Taq_control_genomic_1		50
normal lung	45 Taq_control_genomic_2		50
Crohns colon 403242A	33.18 18 hr. Ascaris lung		44.16
lung 080698-2	30.01 hi dose IL-4 lung		43.59

Table 4 provides TaqMan expression data for rodent, e.g., mouse TNF α .

LIBRARY	Ct_gene	LIBRARY	Ct_gene
L cell	40 rag-1 lung		40
TH1 7 day	40 rag-1 liver		40
TH2 7 day	27.11 rag-1 spleen		23.97
TH1 3 week Balb/C	40 rag-1 thymus		26.29
TH2 3 week Balb/C	26.95 rag-1 kidney		40
preT	40 w.t. Peyer's patches		27.04
D1.1 resting	40 w.t. mesenteric lymph nodes		40
D1.1 con A stim.	40 w.t. colon		26.63
CDC35 resting	40 Braf:ER (-) oligo dT		40
CDC35 con A stim.	39.83 TH1 3 week C57 Bl/6		26.78
Mel 14+ naive T	40 TH2 3 week C57 Bl/6		40
Mel14+ TH1	40 TH1 3 week Balb/C fresh		40
Mel 14+ TH2	31.22 TH2 3 week Balb/C fresh		40
A20	27.39 b.m. DC (YJL) resting		40
CH12	28.18 b.m. DC (YJL) aCD40 stim.		40
Ig. B cell	26.35 b.m. mf + LPS + aIL-10R		40
LPS spleen	21.58 b.m. mf + LPS + IL-10		40
macrophage	40 peritoneal mf		40
J774 resting	24.99 MC-9/MCP-12 pMET7		40
J774 +LPS + anti-IL-10	28.41 EC		40
J774 +LPS + IL-10	27.57 EC + TNF α		40
Nippo-infected lung	26.98 bEnd3 + TNF α		40
IL-10 K.O. spleen	25.43 bEnd3 + TNF α + IL-10		40
IL-10 K.O. colon	23.68 ApoE aorta 5 month		35.16
asthmatic lung	37.45 ApoE aorta 12 month		35.47
w.t. lung	40 NZ B/W kidney		37.17
w.t. spleen	39.95 NZ B/W spleen		25.25
rag-1 heart	40 tolerized & challenged lung		40
rag-1 brain	40 Aspergillus lung		39.26

LIBRARY	Ct_gene	LIBRARY	Ct_gene
rag-1 testes	40	Nippo IL-4 K.O. lung	26.13
Influenza lung	37.13	Nippo anti IL-5 lung	34.73
b common lung 2 month	39.33	w.t. thymus	40
IL-10 K.O. stomach	27.3	w.t. stomach	30.14
IL-10 K.O. MLN aIL-12	40	MM2/MM3 resting pME	40
IL-10 K.O. MLN +IL-10	37.97	MM2/MM3 activated. pME	40
Rag-2 Hh- colon	26.95	Taq_control_water	50
Rag-2 Hh+ colon	22.94	Taq_control_genomic_1	50
IL-7 K.O./Rag-2 Hh- colon	26.77	Taq_control_genomic_2	50
IL-7 K.O./Rag-2 Hh+ colon	24.24	w.t. d17 spinal cord EAE model	40
transfer model IBD	23.01	TNF K.O. d17 spinal cord EAE model	40
w.t. C57 Bl/6 aorta	40	TNF K.O. spinal cord	27.99
w.t. spinal cord	38.8	TNF K.O. spleen	24.93
w.t. C57 Bl/6 spleen	26.38	G.F. ears (skin)	40
w.t. C57 Bl/6 pancreas	40		

The primate, e.g., human, TLR-L1 is expressed in TF-1 cells, D6 cells, and barely detectable in resting U937 cells, resting Jurkat cells, and pooled NK cells. In tissues, it is found in fetal uterus, fetal ovary, allergic lung, and fetal testis. Lower levels are found in fetal kidney, fetal small intestine, fetal brain, fetal adipose tissue, normal lung pool, and fetal lung.

The primate, e.g., human, TLR-L2, TLR-L3, and TLR-L4 seem to be expressed in brain tissue.

The primate, e.g., human, TLR-L5 seems to be expressed in unstimulated A549, activated A549, MRC5, and Bc cell lines. Among tissues, it is most highly expressed in fetal uterus, fetal small intestine, and lesser in fetal lung, fetal kidney, fetal liver, and fetal ovary. It is just detectable in fetal brain, fetal adipose, fetal testes, psoriasis skin, and various intestinal samples.

The 5685C6 probes show positive hybridization to subtraction libraries of Th2 minus Th1 polarized cells, and absence of hybridization to libraries of Th1 minus Th2 polarized cells. This suggests that the probe is present selectively in Th2 polarized cells, and can serve as a marker for such cell type. PCR techniques should confirm the expression profile.

5 Structurally, this protein exhibits similarities to other proteins possessing a thioredoxin fold, including a peroxidase protein, e.g., glutathione peroxidase. See Choi, et al. (1998) *Nature Structural Biol.* 5:400-406. Thioredoxin has been reported to exhibit certain chemoattractant activities. See Bertini, et al. (1999) *J. Expt'l Med.* 189:1783-1789.

10 TaqMan primers were designed for all four novel claudin transcripts. These primer sets were used to screen a panel of human libraries representing different cell types, tissues, and disease states, and two extended cDNA panels. The cDNA panels were composed of samples derived from either normal or diseased human lung or intestine. The claudin genes are some of the most highly regulated genes detected. Moreover, claudin D8 shows the greatest reciprocal regulation between Crohn's and Ulcerative colitis samples, making it a good
15 candidate in future diagnostic panels for these diseases.

claudin-D2: In library southern blots, expression is highest in one Crohn's colon, the fetal intestine, and two epithelial cell lines, lower level expression in fetal lung, kidney, ovary and testes. In human cDNA panels, this is highly up-regulated in 8/9 Crohn's disease, both with and without steroid treatment (mean induction = 53x, n=9). In addition, claudin-D2 is also
20 induced in 9/12 ulcerative colitis samples (mean induction = 8.2x), but this induction is significantly less than that observed in the Crohn's disease samples. Also up-regulated (mean induction=29 x) in 12/13 interstitial lung disease samples (idiopathic pulmonary fibrosis, hypersensitive pneumonitis, and eosinophilic granuloma).

claudin-D8: In library southern blots, expression is highest in fetal kidney and normal
25 colon. Also, expressed in ulcerative colitis colon, thyroid, and fetal lung. No expression is observed in the cells on the panel. In human cDNA panels, high level expression in the gut. Little to no expression in all Crohn's disease samples (mean reduction 130 x, n=9). Some ulcerative colitis samples also have reduced claudin-D8 expression, but the pattern is heterogeneous. In contrast, claudin-D8 is up-regulated in several interstitial lung disease
30 samples (12/15, mean induction = 9x), but the level of expression in these samples is on the

order of ten fold lower than in normal colon. It is also induced in primary human bronchial epithelial cells by I-309.

claudin-D17: In library southern, overall the expression level measured is low relative to the other claudins described here, on the order of 100 fold lower. It is unclear whether the expression level is actually lower or whether the primers for this gene are insensitive (non-optimal). Expression is highest in one of the asthma lungs and in psoriatic skin. No expression is observed in the cell lines on the panel. In human cDNA panels, the expression is increased in 8/11 ulcerative colitis samples (mean induction = 13x), while the expression is unchanged in Crohn's disease samples. Expressed at low level in primary bronchial epithelial cell lines, induced by I-309. Otherwise, level is too low to detect except in sporadic samples.

claudin-D7.2: In library southern, expressed at highest level in human fetal and adult lung, monkey lungs, and in one Crohn's colon sample. Lower level expression in the two epithelial (A549 and CHA) and one fibroblast (MRC5) cell lines on the panel. In human cDNA panels, expressed at a high level in the gut and an even higher level in the lung. Up-regulated in Crohn's disease samples from patients which have not been treated with steroids (mean induction = 3.7x, n=4). No consistent modulation of this gene in any of the lung diseases examined on this panel.

Claudin family structure: If the genomic structural organization of Claudin family members is based upon that of Paracellin-1, then the proteins would all be encoded by 5 exons. The putative splice sites and exon numbers are predictable, corresponding to the residues of D2 about: 2 codons upstream from M1; A43, A75, G129, and C182; and transmembrane segments corresponding to about G17-V36, M83-C104, V117-H141, and L164-Q188. Paracellin has an extra 60 amino acids at its N-terminus, which is located on the cytoplasmic side of the membrane.

Disease Associations: Claudin-D2 is up-regulated in 8/9 Crohn's disease relative to the control samples, while claudin-D8 is down-regulated. All claudins, described in this invention disclosure, show disease association as described above.

The claudins may form part of a diagnostic panel of genes that could distinguish Crohn's disease from ulcerative colitis, or assist in the determination of disease severity in either or both diseases. For example, claudin-D2 is expressed at higher levels in Crohn's disease than in ulcerative colitis. In contrast, the claudin-D8, cluster 1645577, is expressed at

very low levels in Crohn's disease samples, and is less dramatically reduced in most ulcerative colitis samples. See, e.g., Simon, et al. (1999) Science 285:103-106; Hirano, et al. (19xx) Genome Research 10:659-663; Morita, et al. (1999) Proc. Nat'l Acad. Sci. USA 96:511-516; Anderson and Van Itallie (1999) Current Biology 9:R922-R924; and Furuse, et al. (1999) J. Cell Biol. 147:891-903.

Introduction of an adenovirus or another expression vector expressing the claudin-D8 ortholog into the intestines of patients with inflammatory bowel disease may improve intestinal barrier function and ameliorate disease.

In contrast, antibodies to one of the claudins described here may be able to: induce an intracellular signal that could promote tight junction formation and lead to improved intestinal barrier function; block entry of pathogenic agents, which may play a causative role in initiation or maintenance of either Crohn's disease or ulcerative colitis; promote migration of myeloid cells across tight junctions and allow clearance of pathogenic agents prior to infection of the epithelium.

Expression of schlafen family members in fibroblasts/ thymoma cells retards or arrests cell growth. They guide cell growth and T-cell development, and are an integral component of the machinery that maintains T-cell quiescence. They may have important roles in the development or maintenance of autoimmune disorders. The mouse schlafens participate in the regulation of the cell cycle. This family is characterized by two splice variants: a short and a long form.

Schlafen B: 748 aa; ORF. Quantitative PCR analysis reveals in T cells, resting DC, M1 macrophage cell panel. Induced in Hashimoto's thyroiditis, fetal kidney, fetal uterus, and fetal spleen. Slightly induced in Crohn's colon.

Schlafen C: 891 aa, full ORF. Quantitative PCR data revealed this to be significantly up-regulated in all Crohn's samples, asthmatic lung, Ascaris lung, Hashimoto's thyroiditis, and fetal tissues compared to control.

Schlafen D: 578 aa, full ORF. The quantitative PCR data for human schlafen D revealed that it is significantly differentially regulated in Crohn's disease and Ulcerative Colitis compared to normal colon. Also it appears to be highly expressed in many developing tissues (fetal) and disease states (allergic, Ascaris and pneumocystis carinii lungs, Crohn's colon, ulcerative colitis, and Psoriasis skin) compared to cell lines.

Schlafen E: 897 aa, full ORF. Quantitative PCR analysis reveals expression in the colon, fetal liver, fetal lung, fetal ovary, and fetal uterus, and significantly upregulated in one Crohn's sample and highly induced in Hashimoto's thyroiditis.

Schlafen F: 358 aa; full ORF. Distribution analysis is not complete.

5 Similar samples may isolated in other species for evaluation.

V. Cloning of species counterparts

Various strategies are used to obtain species counterparts of, e.g., the DIRS4, preferably from other primates or rodents. One method is by cross hybridization using
10 closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate steps. Another method is by using specific PCR primers based on the identification of blocks of similarity or difference between genes, e.g., areas of highly conserved or nonconserved polypeptide or nucleotide sequence.

15 VI. Production of mammalian protein

An appropriate, e.g., GST, fusion construct is engineered for expression, e.g., in *E. coli*. For example, a mouse IGIF pGex plasmid is constructed and transformed into *E. coli*. Freshly transformed cells are grown, e.g., in LB medium containing 50 μ g/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After overnight induction, the bacteria are
20 harvested and the pellets containing, e.g., the DIRS4 protein, are isolated. The pellets are homogenized, e.g., in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a microfluidizer (Microfluidics, Newton, MA) three times. The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the cytokine receptor protein is filtered and
25 passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0. The fractions containing the DIRS4-GST fusion protein are pooled and cleaved, e.g., with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DIRS4 are pooled and diluted in cold distilled H₂O, to lower the conductivity, and passed
30 back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity

antibody column. Fractions containing the DIRS4 protein are pooled, aliquoted, and stored in the -70° C freezer.

Comparison of the CD spectrum with cytokine receptor protein may suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

5 For other genes, e.g., membrane proteins, the protein may be best expressed on cell surfaces. Those may be in prokaryote expression systems, or eukaryotes. Surface expressed forms will most likely have conformations consistent with the natural interaction with lipid.

VII. Determining physiological forms of receptors

10 The cellular forms of receptors for ligands can be tested with the various ligands and receptor subunits provided, e.g., IL-10 related sequences. In particular, multiple cytokine receptor like ligands have been identified, see, e.g., USSN 60/027,368, 08/934,959, and 08/842,659, which are incorporated herein by reference.

15 Cotransformation of the DIRS4 with putative other receptor subunits may be performed. Such cells may be used to screen putative cytokine ligands, such as the AK155, for signaling. A cell proliferation assay may be used.

In addition, it has been known that many cytokine receptors function as heterodimers, e.g., a soluble alpha subunit, and transmembrane beta subunit. Subunit combinations can be tested now with the provided reagents. In particular, appropriate constructs can be made for 20 transformation or transfection of subunits into cells. Combinatorial transfections of transformations can make cells expressing defined subunits, which can be tested for response to the predicted ligands. Appropriate cell types can be used, e.g., 293 T cells, with, e.g., an NF_b reporter construct.

25 Biological assays for receptors will generally be directed to the ligand binding feature of the protein or to the kinase/phosphatase activity of the receptor. The activity will typically be reversible, as are many other enzyme reactions, and may mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. 30 Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The family of cytokines contains molecules which are important mediators of hematopoiesis or inflammatory disease. See, e.g., Nelson and Martin (eds. 2000) Cytokines in Pulmonary Disease Dekker, NY; Ganser and Hoelzer (eds. 1999) Cytokines in the Treatment of Hematopoietic Failure Dekker, NY; Remick and Friedland (eds. 1997) Cytokines in Health and Disease Dekker, NY; Dinarello (1996) Blood 87:2095-2147; and Thomson (ed. 1994) The Cytokine Handbook Academic Press, San Diego. Ligand and receptors are very important in the signaling process.

VIII. Antibodies specific for proteins

10 Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DIRS4 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

15 Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in situ, for generating an immune response. Serum may be immunoselected to prepare substantially purified antibodies of defined specificity and high affinity.

20 Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the DIRS4, e.g., by ELISA or other assay. Antibodies which specifically recognize specific DIRS4 embodiments may also be selected or prepared.

25 In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (ed. 1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a
30 substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993)

Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-619; and Xiang, et al. (1995) Immunity 2: 129-135.

Moreover, antibodies which may be useful to determine the combination of the DIRS4 with a functional alpha subunit may be generated. Thus, e.g., epitopes characteristic of a particular functional alpha/beta combination may be identified with appropriate antibodies.

IX. Production of fusion proteins

Various fusion constructs are made, e.g., with DIRS4. A portion of the appropriate gene is fused to an epitope tag, e.g., a FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective cytokine receptor. The two hybrid system may also be used to isolate proteins which specifically bind to DIRS4.

X. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, e.g., by generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from populational analysis of variation among individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

XI. Isolation of a ligand for receptor

A cytokine receptor can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. Typically, the binding receptor is a heterodimer of receptor subunits. A binding reagent

is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at $2-3 \times 10^5$ cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of DIRS4-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN₃ for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DIRS4 or DIRS4/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of

buffer plus 4 drops DAB plus 2 drops of H_2O_2 per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

5 Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. The ligand can be immobilized and used to
10 immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DIRS4 fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

15 Phage expression libraries can be screened by mammalian DIRS4. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

20 Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific embodiments
25 that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. A substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 2 (DIRS4); SEQ ID NO: 9, 11, 13, or 53 (TNF α or TNF γ); SEQ ID NO: 15, 17, 19, 21, 23, 25, or 27 (TLR-L1 through TLR-L5); SEQ ID NO: 29 (TGF α); SEQ ID NO: 31 or 33 (5685C6); SEQ ID NO: 35, 37, 39, or 41 (claudins); or SEQ ID NO: 43, 45, 47, 49, or 51 (schlafens).
2. The substantially pure or isolated antigenic polypeptide of Claim 1, wherein said distinct nonoverlapping segments of identity:
 - a) include one of at least eight amino acids;
 - b) include one of at least four amino acids and a second of at least five amino acids;
 - c) include at least three segments of at least four, five, and six amino acids; or
 - d) include one of at least twelve amino acids.
3. The composition of matter of Claim 1, wherein said polypeptide:
 - a) is unglycosylated;
 - b) is from a primate, such as a human;
 - c) comprises at least contiguous seventeen amino acids of said SEQ ID NO;
 - d) exhibits at least four nonoverlapping segments of at least seven amino acids of said SEQ ID NO;
 - e) has a length at least about 30 amino acids;
 - f) has a molecular weight of at least 30 kD with natural glycosylation;
 - g) is a synthetic polypeptide;
 - h) is attached to a solid substrate;
 - i) is conjugated to another chemical moiety; or
 - j) comprises a detection or purification tag, including a FLAG, His6, or Ig sequence.
4. A composition comprising:
 - a) a substantially pure polypeptide of Claim 1;

- b) a sterile polypeptide of Claim 1; or
- c) said polypeptide of Claim 1 and a carrier, wherein said carrier is:
 - i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

5

5. A kit comprising a polypeptide of Claim 1, and:

- a) a compartment comprising said polypeptide; or
- b) instructions for use or disposal of reagents in said kit.

10

6. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a polypeptide of Claim 1, wherein:

- a) said binding compound is in a container;
- b) said polypeptide is from a human;
- c) said binding compound is an Fv, Fab, or Fab2 fragment;
- d) said binding compound is conjugated to another chemical moiety; or
- e) said antibody:

15

- i) is raised to a recombinant polypeptide of Claim 1;
- ii) is raised to a purified polypeptide of Claim 1;
- iii) is immunoselected;

20

- iv) is a polyclonal antibody;
- v) binds to a denatured antigen;
- vi) exhibits a Kd to antigen of at least 30 μ M;
- vii) is attached to a solid substrate, including a bead or plastic membrane;
- viii) is in a sterile composition; or
- ix) is detectably labeled, including a radioactive or fluorescent label.

25

7. A kit comprising said binding compound of Claim 6, and:

- a) a compartment comprising said binding compound; or
- b) instructions for use or disposal of reagents in said kit.

30

8. A method of producing an antigen:antibody complex, comprising contacting under appropriate conditions a primate polypeptide with an antibody of Claim 7, thereby allowing said complex to form.
- 5 9. A method of producing an antigen:antibody complex, comprising contacting under appropriate conditions a polypeptide of Claim 1 with an antibody which binds thereto, thereby allowing said complex to form.
10. A method of producing a binding compound comprising:
- 10 a) immunizing an immune system with a polypeptide of Claim 1; or
- b) introducing a nucleic acid encoding said polypeptide of Claim 1 to a cell under conditions leading to an immune response, thereby producing said binding compound; or
- 15 c) selecting for a phage display library for those phage which bind to said polypeptide of Claim 1.
11. A composition comprising:
- a) a sterile binding compound of Claim 7, or
- 20 b) said binding compound of Claim 7 and a carrier, wherein said carrier is:
- i) an aqueous compound, including water, saline, and/or buffer; and/or
- ii) formulated for oral, rectal, nasal, topical, or parenteral administration.
12. An isolated or recombinant nucleic acid encoding said polypeptide of Claim 1, wherein said:
- 25 a) polypeptide is from a primate; or
- b) said nucleic acid:
- i) encodes an antigenic polypeptide;
- ii) encodes a plurality of antigenic polypeptide sequences of SEQ ID NO:2, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53;
- 30

iii) exhibits identity over at least thirteen nucleotides to a natural cDNA encoding said segment;

iv) is an expression vector;

v) further comprises an origin of replication;

5 vi) is from a natural source;

vii) comprises a detectable label;

viii) comprises synthetic nucleotide sequence;

ix) is less than 6 kb, preferably less than 3 kb;

x) is a hybridization probe for a gene encoding said polypeptide; or

10 xi) is a PCR primer, PCR product, or mutagenesis primer.

13. A cell comprising said recombinant nucleic acid of Claim 12.

14. The cell of Claim 13, wherein said cell is:

15 a) a prokaryotic cell;

b) a eukaryotic cell;

c) a bacterial cell;

d) a yeast cell;

e) an insect cell;

20 f) a mammalian cell;

g) a mouse cell;

h) a primate cell; or

i) a human cell.

25 15. A kit comprising said nucleic acid of Claim 12, and:

a) a compartment comprising said nucleic acid;

b) a compartment further comprising a primate polypeptide; or

c) instructions for use or disposal of reagents in said kit.

30 16. A nucleic acid which:

- a) hybridizes under wash conditions of 30 minutes at 37° C and less than 2M salt to the coding portion of SEQ ID NO: 1, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, or 52; or
- b) exhibits identity over a stretch of at least about 30 nucleotides to a SEQ ID NO: 1, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, or 52.

17. The nucleic acid of Claim 16, wherein:

- a) said wash conditions are at 45° C and/or 500 mM salt; or
- b) said stretch is at least 55 nucleotides.

18. The nucleic acid of Claim 16, wherein:

- a) said wash conditions are at 55° C and/or 150 mM salt; or
- b) said stretch is at least 75 nucleotides.

19. A method of making:

- a) a duplex nucleic acid comprising contacting:
- i) a nucleic acid of Claim 12 with a complementary nucleic acid, under appropriate conditions, thereby resulting in hybridization to form said complex; or
- ii) a nucleic acid complementary to said nucleic acid of Claim 12 with its complementary nucleic acid, under appropriate conditions, thereby resulting in hybridization to form said complex; or
- b) a polypeptide comprising culturing a cell comprising said nucleic acid of Claim 12 under conditions resulting in expression of said nucleic acid.

20. A method of:

- a) modulating physiology or development of a cell comprising contacting said cell with a polypeptide comprising SEQ ID NO: 9, 11, 13, 29, 31, 33, or 53;
- b) modulating physiology or development of a cell comprising contacting said cell with a binding compound of Claim 6 which binds to SEQ ID NO: 9, 11, 13, 29,

31, or 33, thereby blocking signaling mediated by a protein comprising said

SEQ ID NO;

- c) labeling a cell comprising contacting said cell with a binding compound which binds to SEQ ID NO: 2, 15, 17, 19, 21, 23, 25, or 27; or
- 5 d) diagnosing a medical condition comprising a step of evaluating expression of nucleic acid comprising SEQ ID NO: 34, 36, 38, 40, 42, 44, 46, 48, or 50.

SEQUENCE IDENTIFICATION NUMBERS

- SEQ ID NO: 1 is primate DIRS4 nucleotide sequence.
SEQ ID NO: 2 is primate DIRS4 polypeptide sequence.
5 SEQ ID NO: 3 is tissue factor polypeptide sequence.
SEQ ID NO: 4 is primate IFN α β R polypeptide sequence.
SEQ ID NO: 5 is CRF1-4 polypeptide sequence.
SEQ ID NO: 6 is cytor x polypeptide sequence.
SEQ ID NO: 7 is cytor7 polypeptide sequence.
10 SEQ ID NO: 8 is primate TNF α nucleic acid sequence.
SEQ ID NO: 9 is primate TNF α polypeptide sequence.
SEQ ID NO: 10 is rodent TNF α nucleic acid sequence.
SEQ ID NO: 11 is rodent TNF α polypeptide sequence.
SEQ ID NO: 12 is primate TNF γ nucleic acid sequence.
15 SEQ ID NO: 13 is primate TNF γ polypeptide sequence.
SEQ ID NO: 14 is primate TLR-L1 nucleic acid sequence.
SEQ ID NO: 15 is primate TLR-L1 polypeptide sequence.
SEQ ID NO: 16 is rodent TLR-L1 nucleic acid sequence.
SEQ ID NO: 17 is rodent TLR-L1 polypeptide sequence.
20 SEQ ID NO: 18 is primate TLR-L2 nucleic acid sequence.
SEQ ID NO: 19 is primate TLR-L2 polypeptide sequence.
SEQ ID NO: 20 is rodent TLR-L2 nucleic acid sequence.
SEQ ID NO: 21 is rodent TLR-L2 polypeptide sequence.
SEQ ID NO: 22 is primate TLR-L3 nucleic acid sequence.
25 SEQ ID NO: 23 is primate TLR-L3 polypeptide sequence.
SEQ ID NO: 24 is primate TLR-L4 nucleic acid sequence.
SEQ ID NO: 25 is primate TLR-L4 polypeptide sequence.
SEQ ID NO: 26 is primate TLR-L5 nucleic acid sequence.
SEQ ID NO: 27 is primate TLR-L5 polypeptide sequence.
30 SEQ ID NO: 28 is primate TGF α nucleic acid sequence.
SEQ ID NO: 29 is primate TGF α polypeptide sequence.

- SEQ ID NO: 30 is primate 5685C6 nucleic acid sequence.
SEQ ID NO: 31 is primate 5685C6 polypeptide sequence.
SEQ ID NO: 32 is rodent 5685C6 nucleic acid sequence.
SEQ ID NO: 33 is rodent 5685C6 polypeptide sequence.
- 5 SEQ ID NO: 34 is primate claudin-D2 nucleic acid sequence.
SEQ ID NO: 35 is primate claudin-D2 polypeptide sequence.
SEQ ID NO: 36 is primate claudin-D8 nucleic acid sequence.
SEQ ID NO: 37 is primate claudin-D8 polypeptide sequence.
SEQ ID NO: 38 is primate claudin-D17 nucleic acid sequence.
- 10 SEQ ID NO: 39 is primate claudin-D17 polypeptide sequence.
SEQ ID NO: 40 is primate claudin-D7.2 nucleic acid sequence.
SEQ ID NO: 41 is primate claudin-D7.2 polypeptide sequence.
SEQ ID NO: 42 is primate schlafen B nucleic acid sequence.
SEQ ID NO: 43 is primate schlafen B polypeptide sequence.
- 15 SEQ ID NO: 44 is primate schlafen C nucleic acid sequence.
SEQ ID NO: 45 is primate schlafen C polypeptide sequence.
SEQ ID NO: 46 is primate schlafen D nucleic acid sequence.
SEQ ID NO: 47 is primate schlafen D polypeptide sequence.
SEQ ID NO: 48 is primate schlafen E nucleic acid sequence.
- 20 SEQ ID NO: 49 is primate schlafen E polypeptide sequence.
SEQ ID NO: 50 is primate schlafen F nucleic acid sequence.
SEQ ID NO: 51 is primate schlafen F polypeptide sequence.
SEQ ID NO: 52 is rodent TNF γ nucleic acid sequence.
SEQ ID NO: 53 is rodent TNF γ polypeptide sequence.

TissueFactor 1274993R hIFNabR CRF2-4 cytor x cytor7	-METPAWPRVPRPETAVARTLLLGWVFAQVAGASGTTN-T -----MAGPERWGPLLLCLLQAAPGRPR-L MLLSQNAFIF--RSLNLVLMVYISLVFGISYDSPDYT--- -----MAWSLGSWLGGCLLVSALGMV--- --MMP-----KHCFLGFLISFFLTGVAGTQSTHES--- -MRAPGRPAL--RPLPLPPLLLLLLLAAPWGRAVPCVSGGL
TissueFactor 1274993aaR hIFNabR CRF2-4 cytor x cytor7	VAAYNLTWKSTNFKTILEWEPK---PVN-QVYTVQISTKS APPQNVTLLSQNFVSVYLTWLPGLGNPQD-VTYFVAYQSSP DESCTFKISLRNFRSILSWE-LKNHSIVPTHYTLTYTIMS PPPENVRMNSVNFKNILQWESPAFAKGN-LTFTAQYLSY- LKPQRVQFQSRNFHNLQWQPGRALTGNSSVYFVQYKIYG PKPANITFLSINMKNVLQWTPPEGLQGVKVTYTVQYFIYG
TissueFactor 1274993R hIFNabR CRF2-4 cytor x cytor7	--GDWKS--CFYTTDTECDLTDEIVKDVKQTYLARVFSY TRRRWREVEECAGTKELLCSMMCLKKQDLYNKFKGRVRTV KPEDLKVVKNCANTRSFCDLTDEW--RSTHEAYVTVLEG --RIFQDK--CMNTTLTECDFSSLS-KYGDHTL--RVRAE -QRQWKNKEDCWGTQELSCDLTSET-SDIQEPYYGRVRAA -QKKWLNKSECRNINRTYCDLSAET-SDYEHQYYAKVKAI
TissueFactor 1274993R hIFNabR CRF2-4 cytor x cytor7	PAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEO SPSSKS-----PWVESEYLDYLFVEVEPAPP-VLVLTQ FSGNTT-----LFSCSHNFWLAIDMSFEPP-EFEIVG FADEHS-----DWVNIT-FCPVDDTIIGPP-GMQVEV SAGSYS-----EWSMTPRFTPPWETKIDPP-VMNITQ WGTKCS-----KWAESGRFYPFLETQIGPP-EVALTT
TissueFactor 1274993R hIFNabR CRF2-4 cytor x cytor7	VGTKVNVTVEDERTLVR-RNNTFLSLRDVFGKDLIYTLYY T-EEILSANATYQLPP-----CMPPLD---LKYEVAF FTNHINVVKFPSIVE---EELQFDLSLVIE-EQSEGIVK LADSLHMRFLAPKIEN---EYETWTMKNVYN-SWTYNVQY VNGSLLVILHAPNLPYRYQKEKNVSIEDYY--ELLYRVFI DEKSISVVLTAPEKWKRNPEDLPVSMQQIYS-NLKYNVSV

FIG.1A

TissueFactor	WKSSSSG-KKTAKTNTNEFLIDV--DKGENYCFSVQAVIP
1274993R	WKEGAGN-----KVGSSFPAPR--LGPLLHPFLLRFFSP
hIFNabR	KHKPEIK---GNMSGNFTYIIDK-LIPNTNYCVSVYLEHS
CRF2-4	WKNGTDE--KFQITPQYDFEVLRLNLEPWTTCVQVRGFLP
cytor x	INNSLEKEQKVYEGAHRAVEIEA-LTPHSSYCVVAEIIYQP
cytor7	LNTKSNR-TWSQCVTNHTLVLTW-LEPNTLYCVHVESFVP
TissueFactor	SRTVNRKSTDS-PVECMGQEKGE-----FREIFYII
1274993R	-----SQPAPAPLLQEVFPVHS-----
hIFNabR	D---EQAVIKS-PLKCTLLPPGQESESAESAIGGIITVF
CRF2-4	DR--NKAGEWS-EPVCEQTTHDET-----VPSWMVAVIL
cytor x	ML--DRRSQRS-EERCVEIP-----
cytor7	GP--PRRAQPS-EKQCARTLKDQSSEFKAKIIFWYVLPIS
TissueFactor	GAVAFVVIILVIILAI SLHKCRKAG-----
1274993R	-----
hIFNabR	LIALVLTSTIVTLKWIGYICLRNSLPKVLNFHN---FLAW
CRF2-4	MASVFMVCLALLGCFSLWCYKKT-----KY
cytor x	-----
cytor7	IT-VFLFSVMGYSIYRYIHVGKEKHPANLILIIYGNEFDKR
TissueFactor	-----
1274993R	-----
hIFNabR	PFPNLPPLEAMDMVEVIYINRKKKVWDYNYDDES-DSDTE
CRF2-4	AFS-----
cytor x	-----
cytor7	FFVPAEKIVINFITLNI SDDSKISHQDMSLLGKSSDVSSL
TissueFactor	-----VGQSWK-----EN---
1274993R	-----
hIFNabR	AAPRTSGGGYTMHGLTVRPLGQASATSTESQLIDPESEEE
CRF2-4	--PR---NSLPQHLKEFLGHPHNTLLFFSFPLSDEN---
cytor x	-----
cytor7	NDPQPSGNLRPPQEEEEVKHLGYASHLMEIFCDSEENTEG

FIG.1B

TissueFactor	-----SP
1274993R	-----
hIFNabR	PEEDYSSTEGSGGRITFNVDLNSVFLRVLDDEDSDDLEAP
CRF2-4	-----VFDK
cytor x	-----
cytor7	SLQEEVSTQGTLLLESQAALAVLGPQTLQYSYTPQLQDLDP
TissueFactor	-----
1274993R	-----
hIFNabR	PDLPEVDVELPTMPKDSP-QQLELLSGPCERRKSPLQDPF
CRF2-4	-----D-----
cytor x	-----
cytor7	TSLTQQESLSRTIPDPKTVIEYEYDVRTTDICAGPEEQEL
TissueFactor	LNVS-----
1274993R	-----
hIFNabR	LMLSSHLEEMVDPEDPDNVQSNHLLASGEG-----TQ
CRF2-4	LSVIAEDSESG-KQNP-----G-----DS
cytor x	-----
cytor7	LAQEHTDSEEGPEEEPPSTTLVDWDPQTGRLCIPSLSSFDQ
TissueFactor	-----
1274993R	-----
hIFNabR	PTFPSPSSEG-----LWSEDAPSDQSDTSES
CRF2-4	CSLGTPPGQG-----PQS-----
cytor x	-----
cytor7	DSEGCEPSEGDGLGEEGLLSRLXEEPAPDRPPGENETYLM
TissueFactor	-----
1274993R	-----
hIFNabR	DVDLGDGYIMR---
CRF2-4 aa	-----
cytor x	-----
cytor7	QFMEEWGLYVQMEN

FIG.1C

pTNF-x	1		AGREGEE-	7
rTNF-x	1	MWAWGAAAAALLWLQTAGAGARQELKKSRLQLEFARVDSPNITTSNREGFPG		50
pTNF-y	1			0
pTNF-x	8	---PSQASGPEFSDAHMTWLNFRPPDDGALRKRCGRDCKKPR---	DLFG	51
rTNF-x	51	SVKPEASGPELSDAHMTWLNFRPPDDGSSRKRCGRDCKKSRLSGLPG		100
pTNF-y	1			0
pTNF-x	52	PPGPPG-----AEVTAETLLHEFQELLKEATERRRFSGLLDPLPQG		92
rTNF-x	101	PPGPPGPPGPPGSPGVGVTPEALLQEFQELLKEATELRFSGLPDPTLLPQE		150
pTNF-y	1			0
pTNF-x	93	RGLRLVGEAFHCRLLQGPRRVDKRTLVELHGFQAPAAQGAFLRGSLSLAS		142
rTNF-x	151	PSQRLVVEAFYCRLKGPVLVDKTKTLVELQGFQAPTQGAFLRGSLSLSL		200
pTNF-y	1	HELGVYYLPDAEGAFRRRGPGGLNLTS		25
pTNF-x	143	GRFTAPVSGIFQFSASLHVDHSELQKGKARLRARDVVCVLICIESLCQRHT		192
rTNF-x	201	GRFTAPVSAIFQFSASLHVDHSELQGRGLRTRDMMRVLICIESLCHRHT		250
pTNF-y	26	GQYRAPVAGFYALAAATLHVALGEPFRRGPPRPDRDHLRLLLICIQSRCQRNT		75
pTNF-x	193	CLEAVSGLESNSRVFTLQVQGLLQLAGQYASVFVDNGSGAVLTIQAGSS		242
rTNF-x	251	SLEAVSGLESNSRVFTVQVQGLLHLQSGQYVSFVDNSSGAVLTIQNTSS		300
pTNF-y	76	SLEAIMGLESSSELTFTISVNGVLYLQMGQWTSWACERPP-QALPLRGKWS		124
pTNF-x	243	FSGLLLT	250	
rTNF-x	301	FSGMLLT	308	
pTNF-y	125	TDLDNVWTVSE	135	

FIG. 2

TLRL1_HU -----MLSG---VFSLSVLTVAGILQTES-----RKTAKDICKIRCLCEEKENVLNIN
 TLRL2_HU -----MLQT---LAFAVTSLVLSCAET-----IDYGEICDNACPCEEKDGILTVS
 TLRL4_HU -----MFLW---LFLILSALISSTNAD-----SDISVEICN-VCSCSVENVVLYVN
 TLRL3_HU MKPSIAEMLHRGRMLWIIILLSTIALGWTTPIPIEDSEIDEPCFDPICYCEVKESLFHIIH
 TLRL5_HU -----MKLWIHLFYSSLLACISLSHSQTP-----VLSSRGSCDSLNCNCEEKDGTMLIN
 * . : * * * * : : :

TLRL1_HU CENKGETTVSLLQPQYRIYQLFNLGNLLTRLYPNEFVNYNAVTLHLGNNGLQEI RTGA
 TLRL2_HU CENRGIISLSEISPPRFPPIYHLLLSGNLLNRLYPNEFVNYTGASILHLGSNVIQDIETGA
 TLRL4_HU CEKVSYPNPQLKPPWSNFYHLLNFQNNFNILYPNTFLNFESHAVSLHLGNKLNQIEGGA
 TLRL3_HU CDSKGETNISQITEFWSRPFKLYLQNRSMRKLYTNSFLHLNNAV SINLGNALQDIDIQTGA
 TLRL5_HU CEAKGIKMVSEISVPPSRPFQLSLLNGLTMLHTNDFSGLTNAISIH LGFNNIADIEIGA
 * : . . : : * : * : * : * : * : * : * : * : * : *

TLRL1_HU FSGLKT LKRLHLNKNKLEILREDTFGLGLESLEYLQADYNYISAIEAGAFSKLNKLVLLIL
 TLRL2_HU FHGLRGLRRLHLNKNKLEILLRDDTFGLGLENLEYLQVDYNYISVIEPNAFGKLHLLQVLIL
 TLRL4_HU FLGLSALKQLHLNKNELKILRADTFGLGIENLEYLQADYNLIKYIERGAENKHLKLVLLIL
 TLRL3_HU FNGLKILKRLYLHENKLDVFRNDTFGLGLESLEYLQADYNVIKRIESGAFRNLSKLRVLIL
 TLRL5_HU FNGLGLLKQLHINHNSLEILKEDTFHGLENLEFLOADNNFITVIEPSAFSKLNRLKVLIL
 * * * * * : : : : : * * * * * : : : : : * * * * * : : : : *

FIG. 3A

TLRL1_HU NDNL LSLPSNVFRFVLLTHLDLRGNRLKVMFPAGVLEHIGG-IMEIQLEENPWNCDCDL
 TLRL2_HU NDNL LSSLPNNLFRFVPLTHLDLRGNRLKLLPYVGLLQHMDK-VVELQLEENPWNCCEL
 TLRL4_HU NDNL ISFLPDNIFREASLTHLDLRGNRIQKLPYIGVLEHIGR-VVELQLEDNPWNCSCDL
 TLRL3_HU NDNL IPMLPTNLFKAVSLTHLDLRGNRLKVLFYRGMLDHI GRSLMELQLEENPWNCCTCEI
 TLRL5_HU NDNAIESLPPNIFRFVPLTHLDLRGNQLQTLPYVGELEHIGR-ILDLQLEDNKWACNCDL
 *** ; ** *:* . *****:***: : : *:*: . : : : *:*: * * * *:

TLRL1_HU LPLKAWLDTIT--VFVGEIVCETPFRLHGKDVLTQLTRQDLCPRKSASDSSQRGSHADTHV
 TLRL2_HU ISLKDWLDSISYSALVGDVVCETPFRLHGRDLDEVSKQELCPRRLLISDYEMRPQTPLSTT
 TLRL4_HU LPLKAWLENMPYNIYIGEAI CETPSDLYGRLLKETNKQELCPMGTGSDFDVR-ILPPSQL
 TLRL3_HU VOLKSWLERIPYALVGDI TCETPFHFHKGDLREIRKTELCPLLSDSEVEASLGIPHSSS
 TLRL5_HU LQLKTWLENMPPQSIIGDVVCNSPPFFKGSILSRLLKESICPTPPVYEEHED-----PSGS
 ; ** **: :. :*: :*: : * : : : : * : : : : *

TLRL1_HU QRLSPT---MNPALN-----PTRAPKASRPP-KMRNRPTPR-VTVSKDRQSF
 TLRL2_HU GYLHTTPASVNSVATSSA-----VYKPPLKPPKGTQPNKPRVPTSRQPSKDLGYSNY
 TLRL4_HU ENGYTTPNGHTTQTS-----LHRLVTKPKTTNPS-----KISGIVAGKALSNRNL
 TLRL3_HU SKENAWPTKPSMLSSVHFTASSVEYKSSNKQPKTKQP---RTPRPPSTSQALYPGPNO
 TLRL5_HU LHLAATSSINDSRMS-----TKTTSILKLP-----TKAPGL
 . . . :

FIG. 3B.

TTRL1_HU	NYLQTVYKNDLLEYSSDLLHLGNNR	IAVIOEGAFTNL	TSLRRLYLNGNYLEVLYPSMFD
TTRL2_HU	NYIAVVRRTDFLEATGLDLLHLGNNR	ISMIQDRAFGDLT	NLRRLYLNGNRIERLSPELFY
TTRL4_HU	NSIKDVDVSFTDFEGLDLLHLSNQIT	VTKGDVFHNLT	NLRRLYLNGNQIERLYPEIES
TTRL3_HU	NLIQKIYRSDFWNFSSDLLHLGNNR	ISYVDGAFINLP	NKSLFNGNDIEKLTPGMFR
TTRL5_HU	NIIHSLMKSDLVEYFTLEMHLGNNR	IEVL EEGSFMNLTR	LQKLYLNGNHLLTKLSKGMFL
	* ; . : * :	** ** *	: * : * : *

TLRL1_HU	GLQSLQYLYEYNVIKEIKPLTFDALINQLQLFLNNNLLRSLPDNIFGGTALTRLNLRNN
TLRL2_HU	GLQSLQYLFQYNLIREIQSGTFDPVPNLQLQLFLNNNLLQAMPSCGVFSGLTLLRLNLRSN
TLRL4_HU	GLHNLQYLYEYNLIKEISAGTFDSMPNLQLLYLNNLLKSLPVYIFSGAPLARLNLRNN
TLRL3_HU	GLQSLHYLYFEFNVIREIQPAAFSLMPNLKLLFLNNNLLRTLPTDAFAGTSLARLNLRKN
TLRL5_HU	GLHNLEYLYEYNAIKEILPGTFNMPKLVLYLNNLLQVLPPHIFSGVPLTKVNLRKTN

FIG. 3C

TLRL1_HU HFSLPVKGVLDQLPAFIQIDLQENPWDCTCDIMGLKDWTEHANSPVIINEVTCESPAKH
TLRL2_HU HFTSLPVSGVLDQLKSLIQIDLDHNPWDCTCDIVGMKLVVEQLKVGVLVDEVICKAPKKE
TLRL4_HU KEMVLPVSGVLDQLQSLTQIDLEGNPWDCTCDLVALKLWVEKLSGDIWVKELKCEPVOF
TLRL3_HU YFLVLPVAGVLEHLNAIVQIDLNENPWDCTCDLVPEFKQWIEIISVSVVGDVLCRSPENL
TLRL5_HU QFTHLPVSNILDDLTLTQIDLEDNPWDSCDLVGLQQWIKLSKNTVTDDILCTSPGHL
* *** .:*. * : ****. *****: : * : : * : * :
AGEILKFLGREAI CPD-----SPNLSGTVLSMNHNTDTPRSLVS--PSSYPELH--
AETDMRSIKSELLCPDYSDVVSTPTPSSIQVPARTSAVTPAVRLNSTGAPASLGAGGGA
ANIELKSLKNEILCPK-----LNKPSAPFTSPAPAITFTTPLGPIRSPPGG--
THRDVRTIELEVLCPD-----MLHVAPAGESPAQPGDSHLIGAPTSASPYEFSPPG--
DKKELKALNSEILCPG-----LVNPNMPTQTSYLMVTPATTNTADTILRSLT
:: : * : ** . . .
TEVPLSVLILGLLVFVILSVCFGAGLFVFLKRR-KGVPSVPRNTNNDVSSFQYQGSY
SSVPLSVLILSLLLVFIMSVFVAAGLFVLMKRR-KKNQSDHTSTNNSDVSSFNMQYSVY
-PVPLSILILSVLILITVFVAFCLLVFVLRN-KKPTVKHEGLGNPDGSMQLQLRKH
GPVPLSVLILSLLLVFFSAVFVAAGLFAYVLRRRRKKLPFRSKRQEGVDLTGIQMQRHL
DAVPLSVLILGLLIMEITIVFCAAGIVVLVLRN-RRYKKKQVDEQMRDNSPVHLQYSMY
*****:*****: * . . . * : * : * : *

FIG. 3D.

TLRL1_HU	N-----TETHDK-----TDGHVYNYIPPPVGOMCQNPIMQKEGDPVAYYR
TLRL2_HU	GGGGTGGHPAHVHHRGPALPKVKTPEGHVYEYIPHPLGHMCKNPIYRSREGNSVEDYK
TLRL4_HU	D-----HKTNKK-----DGLSTEAFIPQTIEQMSKSHTCGLKESETGFMFS
TLRL3_HU	FEDGGGGGGGGRRPTLSSPEKAPPVGHVYEYIPHPVTQMCNNPIYKPREEEEVAVSS
TLRL5_HU	G-----HKTHHTTE-----RPSASLYEQHMVSPMVHVYRSPSFGPKHLEEEERN

TLRL1_HU	NLQE-----FSYSN-----LEEKKEEP-----
TLRL2_HU	DLHE-----LKVTYSSNHHLQQQQPPPPPPQQQ-
TLRL4_HU	DPPG-----QKVVMRN-----VADKEKDLLH-----
TLRL3_HU	AQEAESAERGPGTQPPGMGEALLGSEQFAETPKENHSNYRTLLEKEKEWALAVSSQLN
TLRL5_HU	EKEG-----SDAKHLQRSLLLEQENHSP-----

TLRL1_HU	-----ATPAYTISATELLEK-----QATP-----REPELLYQNIA
TLRL2_HU	--PPPQLQLQPGEEERRESHLRSPAYSVSTIEPRED-----LLSPV---QDADRFYRGIL
TLRL4_HU	-----VTRKRLSTIDELDE-----LFPS-----RDSNVFIQNEL
TLRL3_HU	TIVTVNHHHPHAPGVGVGGTGGDLAGERHHEKNGGVLFPPGGCGCGSMMLLDRE
TLRL5_HU	-----LTGSNMKYKTTNQSTE-----FLS---FQDASSLYRNIL

FIG. 3E

TLRL1_HU	ERVKELPS--AG--LVHYN--FCTLPKRQFAPSYESRRQNQ-----DRINKTVLYGT
TLRL2_HU	EPDKHCSTTPAGNSLPEYPKFFPCSPAAYTFSPNYDLRRPHQYLHPGAGDSRLREPVLSP
TLRL4_HU	ESKKEYNS-----IGVSGFEIRYPEKQPKD-----KSKKSLIGGN
TLRL3_HU	RPQPAPCTVGFVDCLYGTVPKCLKELHVPQGMQYPDLOQDA-----RLKETLLFSA
TLRL5_HU	EKERELQQLG-----ITEYLRKNIAQLQPDMEAHYPGAHEEL-----KLMETLMYSR

* ; :

TLRL1_HU	PRKCFVGQS-KPNHPLLQAKPQSEPDYLEVLEKQTAISQL
TLRL2_HU	PSAVFVEPN-RNEYLELKAKLNVEPDYLEVLEKQTTFSEQ
TLRL4_HU	HSKIVVEQR-KSEYFELKAKLQSSPDYLOVLEEQTALNKI
TLRL3_HU	EKGFTDHQTQKSDYLELRAKLQTKPDYLEVLEKTTYRF--
TLRL5_HU	PRKVLVEQT-KNEYFELKANLHAEPDYLEVLEQQT-----

: :: *::: : . *****: *

FIG. 3F

D2	1	MASGLQLVGYILGLLGLTLVAMLLPSWKTSSYVGASIVTAVGFSKGL	50
D8	1	MATHALEIAGLFLGGVGMVGTVAVTVMQPWRVSAFIENNI VFFENFWEGL	50
D17	1	MAFYPLQIAGLVGLGMVGTLATTL PQRVSAFVGSNI IVFERLWEGL	50
D7.2	1	MAVTACQGLGFVVSLLIGIAGIIAATCMAQWSTQDLY -NNPVTAVFNYQGL	49
	**	. * . * . * . *	**
D2	51	WMECATHSTGITQCDIYSTLLGLPADIQGAQAMVTS SAISSLACIISVV	100
D8	51	WMNCVRQANIRMQCKIYDSSLALSPDLQAARGLMCAASVMSFLAFEMMAIL	100
D17	51	WMNCIRQARVRLQCKFYSSLLALPPALETARALMCVAVALSLLALLIGIC	100
D7.2	50	WRSCVRESSGFTECRGYFTLLGLPGKGQ-----VSCWLEGEI	86
	*	* . * * * *	.
D2	101	GMRCTVFCQES-RAKDRVAVAGGVFFILGGLLGEIPVAWNHLHGILRDFYS	149
D8	101	GMKCTRCTGDNEKVKAHILLTAGINLIITGMVGANPVNLVSNAIIRDFFT	150
D17	101	GMKVQCTGSNERAKAYLLGTSGVLFILTGIFVLI PVSWTANIIIRDFYN	150
D7.2	87	GG-----GEE-----TAGSVWAPRQGLLGRE-----ELRFVFDGRN	117
	*	. . . *	*

FIG. 5A

D2 150 PLVPDSMKFEIGEALYLGIISLFLIAGIILCFSCSSQNRNRSNYDAYQ 199
D8 151 PIVNVAQKRELGEALYLGWTTALVLIVGGALFCCVFCCNEKSSSYRYSIP 200
D17 151 PAIHIGQKRELGAALFLGWASAAVLFIGGLLCGFCCCNRRKKQGYRYPVP 200
D7.2 118 SHLHQGG-----IGG-----RE-----P 130

.

*

D2 200 AQPLATRSSPRAGQPPKVKSEFNSYSLTGYV 230
D8 201 SHRTTQKSYHTGK-----KSPSVYSRSQYV 225
D17 201 GYRVPHTDKRRN-----TTMLSKTSTSYV 224
D7.2 131 130

FIG. 5B


```
B      1  MESLKTDEMPYPEVIVDVGRVIFGEENRKKMTNSCLKRSENSRIIRA 48
C      1  MEANHCSLGVYPSYFDLVIDVGEVTLGEENRKKLQKTQDQ-ERARVIRA 49
D      1  MNISVDLETNYAELVLDVGRVTLGENSRKKMKDKLKKQNERVVSRA 47
E      1  MSLRIDVDTNFPECVVDAGKVTLGTQQRQEMDPRLEK-QNEIILRA 46
F      1  MEANQCPLVVEPSYFDLVINVGEVTLGEENRKKLQKIQRDQ-EKERVMRA 49
      . . . . * * * * * . . . . * *
      . . . . * * * * * . . . . * *

B      49 ICALLNSGGGVKAEIDDKTYSYQCHGLGDLETQKLLPS-GSQKYLD 97
C      50 ACALLNSGGGVQIOMEMANR--DERPTMGLDLEESLRKLIQYPYLAFFE 97
D      48 MCALLNSGGGVKAEIENEDYSYTKDGI GLDLENSFSNILLF-VP-EYLD 95
E      47 VCALLNSGGGIIKAEIE-----NKGYNERHGVGLDVPPPIFRSHLD 87
F      50 ACALLNSGGGVIRMAKK-----VEHPVEMGLDLEQSLRELIQSSDLQAFFE 95
      ***** *
      * * * * *

B      98 YMQQGHNLLIFVKWSWD-----VFSLPLRICSLRSLNLYRRDVTSAINLSA 143
C      98 TKQHGRCFYIFVKWSWDGPFELKDGFSNRSICLSSSLYCRSGTSVLHMNS 147
D      96 FMQNGNYFLIFVKWS-----INTSGLRITLSSNLYKRDITSKVMNA 139
E      88 KMQKENHFLIFVKSWNTEAGVP-----LATLCSNLYHRERTSTDVMS 130
F      96 TKQQGRCFYIFVKWSWGPFEPEDRSVKPRCLCSLSSSLYRRSETSVSRMSDS 145
      *****
      * * * * *
      . . . * * * * * * . . .
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FIG. 6A

B 144 SSALELIREKGFRAQRPRVKLHPQQVLNRCIQEEDMR-----ILA 187
C 148 RQAFDFLTKER-QSKYNLINEGPPSKIMKAVYQNI SESN-----PA 189
D 140 TAALEFLKD--MKKTRGRLYLRPELLAKRPCVDIQEENMK-----ALA 181
E 131 QEALAFKCR--QTPTNINVSNSLGPQAAQGSVQYEGNIN-----VSA 172
F 146 REAFCEFLKTR----KPKILEEG-PFHKIHKG VYQELPNSDPADPNSDPA 190
* * * *

B 188 SEFFKKDKL MYKEKLNFTSTHVEFKRFTTKKVIPIKEMLPHYVS AFAN 237
C 190 YEVEQTD TIYGEILSFPEPSIEFKQFSTKHQQYVENI IPEYISAFAN 239
D 182 GVFFDRTELDRKEKLTFTSTHVEIKNFSTTEKLLQRIKEIL PQYVS AFAN 231
E 173 AALFDRKRLQYLEKLNLPSTHVEFVMFST-DVSHCVKDRLPKCVS AFAN 221
F 191 DLIFQKDYLEYGEILPFPESQLVEFKQFSTKHFEYVKRTIPEYVPAFAN 240
* * * * *

B 238 TQGGYVLIGVDDKSKEVVGCKWEKVNPDLLKKEIENCI EKLPTEHFCEK 287
C 240 TEGGYLFIGVDDKSRKVLGCAKEQVDPDSLKNVIARAI SKLPVHFCSSK 289
D 232 TDGGYLFIGNED-KEIIGFKAEMSDLLDLEREIEKSI RKMVPVHFCMEK 280
E 222 TEGGYVFFGVHDETCQVIGCEKEKIDLTSLRASIDGCI KKL PVHFFCTQR 271
F 241 TGGYLFEXGVDDKSREVLGC AKENXDPDSL RXKIE XAIYKLPCXHF CQPQ 290
* * * * *

FIG. 6B

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B 288 PKVNETTKILNVYQKDVLDGYVCVIOVEPFCCVFAEAPDSWIMKDNSVT 337
C 290 PRVEYSTKIVEVFCGKELYGLCVIKVKAFCVVFSEAPKSMVREKYIR 339
D 281 KKINYSCKFLGVYDKGSLCGYVCALRVERFCCAVFAKEPDSWHVKNRVM 330
E 272 PEIKYVNLNELEVHDKGALRGYVCAIKVEKFCCAVFAKVPSSWQVKDNVR 321
F 291 RPITFTLKIVDLKRGELYGYACMIRVNPFCFCAVFAEAPNSWIVEDKYVC 340
      . . . * * * * . . . * * * * . . . * * * * .
B 338 RLTAEQWVVMMLDTQ----- 352
C 340 PLTTEEWVEKMMADPEFPDFAEAFESQLSLSDSPSLCRPVYSKKGLEH 389
D 331 QLTRKEWIOFMVEAEPKFS--SSYEEVISQINTSLPAPHSWPLL-----EW 374
E 322 QLPTREWTAWMEADPDLS---RCPEMVLQSLSSATPRSKPVCIHKNSEC 369
F 341 SLTTEKWVGMMTDTDPDLL-QLSEDFECQLSSGPPLSRPVYSKKGLEH 389
      * * * * *
B 353 -----SGKGK 357
C 390 KADLQQHLFPVPPGHLECTPESLWKELSLQHEGLKELIHKQMRPFSQGIV 439
D 375 QR--QRHHCPLSGRITYTPENLCRKLFLQHEGLKQLICEEMDSVRKGS 422
E 370 LKEQQKRYFPVFSDRVVYTPESLYKELFSQHKGLRDLINTEMRPFSQGIL 419
F 390 KKELQQLLESVPVPGYLRYTPESLWRDLISEHRGLEELINKQMOPFFRGIV 439
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FIG. 6C

B	358		357
C	440	ILSRWAVDNLQEKPGVICDALLIAQNSTPILYTIILREQDAEGQDYCTR	489
D	423	IFSRWSVDLGLQENHKVLC DALLISQDSPVLVYTFHVMVQDEEFKGYSTQ	472
E	420	IFSQSWAVDNLGLQEKQGVICDALLISQNNTPILYTI FSKWDAGCKGYSMI	469
F	440	ILSRWAVDNLQEKPGVICDALLIAQNSTPILYTIILREQDAEGQDYCTR	489
B	358		357
C	490	TAFTLKQKLVNMGGYTGKVCVRAKVLCLSPESAEAEAAVSPMDYPASY	539
D	473	TALTLKQKLA KIGGYTKKVCVMTKIFYLSPEG-----	504
E	470	VAYSLKQKLVNKG GYTGRLCITPLVCVLNSDRKAQSVYSSY-LQIYPESY	518
F	490	TAFTLKQKLVNMGGYTGKVCVRAKVLCLSPESAEAEAAVSPMDYPASY	539
B	358		357
C	540	SLAGTQHMEALLQSLVIVLLGFRSLLSDQLGCEVLNLLTAQQYEIFSRSL	589
D	505	-----MTSCQYDLRSQVI	517
E	519	NFMTPQHMEALLQSLVIVLLGFKSFLSEELGSEVLNLLTNKQYELL SKNL	568
F	540	SLAGTQHMEALLQSLVIVLLGFRSLLSDQLGCEVLNLLTAQQYEIFSRSL	589

FIG. 6D

B	358		357
C	590	RKNRELFVHGLPGSGKTIAMKIMEKIRNVFHC	639
D	518	YPESYFTRRKYLLKALFKALKRLKSLRDQSF	559
E	569	RKTRELFVHGLPGSGKTIILALRIMEKIRNVF	618
F	590	RKNRELFVHGLPGSGKTIAMKIMEKIRNVFHC	639
B	358		357
C	640	ISD--RNICRAETRETFLEKFEHIQHI	687
D	560	-----IDCFQNDKKMFKSCRR	577
E	619	VSESKNICQPVTRKTFMKNNEFEHIQHI	668
F	640	ISD--RNICRAETRKTFLENFEHIQHI	687
B	358		357
C	688	TQREKDCPGVLWIFLDYFQTSHLGSLPPL	737
D	578	T	578
E	669	TRQQRDGPVGLWIFLDYFQTYHLSCSGL	718
F	688	TRRAKGGPGILWIFLDYFQTSHLDCSGL	737

FIG. 6E

B	358		357
C	738	AEYIQQEMQLIIENPPINIPHGYLAILSEAKWVPGVPGNTKIIKNFTLEQ	787
D	579		578
E	719	ANYLQQVMQEARQNPPNLPFGSLVMLYEPKWAQGVPGNLEIIEDLNLEE	768
F	738	AKYLQKENASN	748
B	358		357
C	788	IVTYVADTCRCFFERGYSPKDVAVLVSTVTEVEQYQSKLLKAMRKK----	833
D	579		578
E	769	ILIIYVANKCRFLLRNGYSPKDIAVLFTKASEVEKYKDRLLTAMRKRKLSQ	818
F	749		748
B	358		357
C	834	-----MVVQLSDACDMLGVHIVLDSVRRFSGLESIIVEGHPRTADPAI	877
D	579		578
E	819	LHEESDLLLIQIGDASDVLTDHIVLDSVCRFSGLERNIVEGINPGVAPPAG	868
F	749		748

FIG. 6F

B	358		357
C	878	LPNIIICLASRAKQHLIYIFL	897
D	579		578
E	869	AYNLLIICLASRAKRHLIYILKASV	891
F	749		748

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35 40 45

Asn Pro Gln Asp Val Thr Tyr Phe Val Ala Tyr Gln Ser Ser Pro Thr
50 55 60

Arg Arg Arg Trp Arg Glu Val Glu Glu Cys Ala Gly Thr Lys Glu Leu
65 70 75 80

Leu Cys Ser Met Met Cys Leu Lys Lys Gln Asp Leu Tyr Asn Lys Phe
85 90 95

Lys Gly Arg Val Arg Thr Val Ser Pro Ser Ser Lys Ser Pro Trp Val
100 105 110

Glu Ser Glu Tyr Leu Asp Tyr Leu Phe Glu Val Glu Pro Ala Pro Pro
115 120 125

Val Leu Val Leu Thr Gln Thr Glu Glu Ile Leu Ser Ala Asn Ala Thr
130 135 140

Tyr Gln Leu Pro Pro Cys Met Pro Pro Leu Asp Leu Lys Tyr Glu Val
145 150 155 160

Ala Phe Trp Lys Glu Gly Ala Gly Asn Lys Val Gly Ser Ser Phe Pro
165 170 175

3

Ala Pro Arg Leu Gly Pro Leu Leu His Pro Phe Leu Leu Arg Phe Phe
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Ser Pro Ser Gln Pro Ala Pro Ala Pro Leu Leu Gln Glu Val Phe Pro
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Val His Ser
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Ser Gly Thr Thr Asn Thr Val Ala Ala Tyr Asn Leu Thr Trp Lys Ser
 35 40 45

Thr Asn Phe Lys Thr Ile Leu Glu Trp Glu Pro Lys Pro Val Asn Gln
 50 55 60

Val Tyr Thr Val Gln Ile Ser Thr Lys Ser Gly Asp Trp Lys Ser Lys
 65 70 75 80

Cys Phe Tyr Thr Thr Asp Thr Glu Cys Asp Leu Thr Asp Glu Ile Val
 85 90 95

Lys Asp Val Lys Gln Thr Tyr Leu Ala Arg Val Phe Ser Tyr Pro Ala
 100 105 110

Gly Asn Val Glu Ser Thr Gly Ser Ala Gly Glu Pro Leu Tyr Glu Asn
 115 120 125

Ser Pro Glu Phe Thr Pro Tyr Leu Glu Thr Asn Leu Gly Gln Pro Thr

4

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Asp Glu Arg Thr Leu Val Arg Arg Asn Asn Thr Phe Leu Ser Leu Arg		
	165	170 175
Asp Val Phe Gly Lys Asp Leu Ile Tyr Thr Leu Tyr Tyr Trp Lys Ser		
	180	185 190
Ser Ser Ser Gly Lys Lys Thr Ala Lys Thr Asn Thr Asn Glu Phe Leu		
	195	200 205
Ile Asp Val Asp Lys Gly Glu Asn Tyr Cys Phe Ser Val Gln Ala Val		
	210	215 220
Ile Pro Ser Arg Thr Val Asn Arg Lys Ser Thr Asp Ser Pro Val Glu		
	225	230 235 240
Cys Met Gly Gln Glu Lys Gly Glu Phe Arg Glu Ile Phe Tyr Ile Ile		
	245	250 255
Gly Ala Val Ala Phe Val Val Ile Ile Leu Val Ile Ile Leu Ala Ile		
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Ser Leu His Lys Cys Arg Lys Ala Gly Val Gly Gln Ser Trp Lys Glu		
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Asn Ser Pro Leu Asn Val Ser		
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Asp Tyr Thr Asp Glu Ser Cys Thr Phe Lys Ile Ser Leu Arg Asn Phe
 35 40 45

Arg Ser Ile Leu Ser Trp Glu Leu Lys Asn His Ser Ile Val Pro Thr
 50 55 60

His Tyr Thr Leu Leu Tyr Thr Ile Met Ser Lys Pro Glu Asp Leu Lys
 65 70 75 80

Val Val Lys Asn Cys Ala Asn Thr Thr Arg Ser Phe Cys Asp Leu Thr
 85 90 95

Asp Glu Trp Arg Ser Thr His Glu Ala Tyr Val Thr Val Leu Glu Gly
 100 105 110

Phe Ser Gly Asn Thr Thr Leu Phe Ser Cys Ser His Asn Phe Trp Leu
 115 120 125

Ala Ile Asp Met Ser Phe Glu Pro Pro Glu Phe Glu Ile Val Gly Phe
 130 135 140

Thr Asn His Ile Asn Val Val Val Lys Phe Pro Ser Ile Val Glu Glu
 145 150 155 160

Glu Leu Gln Phe Asp Leu Ser Leu Val Ile Glu Glu Gln Ser Glu Gly
 165 170 175

Ile Val Lys Lys His Lys Pro Glu Ile Lys Gly Asn Met Ser Gly Asn
 180 185 190

Phe Thr Tyr Ile Ile Asp Lys Leu Ile Pro Asn Thr Asn Tyr Cys Val
 195 200 205

Ser Val Tyr Leu Glu His Ser Asp Glu Gln Ala Val Ile Lys Ser Pro
 210 215 220

Leu Lys Cys Thr Leu Leu Pro Pro Gly Gln Glu Ser Glu Ser Ala Glu
 225 230 235 240

Ser Ala Lys Ile Gly Gly Ile Ile Thr Val Phe Leu Ile Ala Leu Val
 245 250 255

Leu Thr Ser Thr Ile Val Thr Leu Lys Trp Ile Gly Tyr Ile Cys Leu
260 265 270

Arg Asn Ser Leu Pro Lys Val Leu Asn Phe His Asn Phe Leu Ala Trp
275 280 285

Pro Phe Pro Asn Leu Pro Pro Leu Glu Ala Met Asp Met Val Glu Val
290 295 300

Ile Tyr Ile Asn Arg Lys Lys Lys Val Trp Asp Tyr Asn Tyr Asp Asp
305 310 315 320

Glu Ser Asp Ser Asp Thr Glu Ala Ala Pro Arg Thr Ser Gly Gly Gly
325 330 335

Tyr Thr Met His Gly Leu Thr Val Arg Pro Leu Gly Gln Ala Ser Ala
340 345 350

Thr Ser Thr Glu Ser Gln Leu Ile Asp Pro Glu Ser Glu Glu Glu Pro
355 360 365

Asp Leu Pro Glu Val Asp Val Glu Leu Pro Thr Met Pro Lys Asp Ser
370 375 380

Pro Gln Gln Leu Glu Leu Leu Ser Gly Pro Cys Glu Arg Arg Lys Ser
385 390 395 400

Pro Leu Gln Asp Pro Phe Pro Glu Glu Asp Tyr Ser Ser Thr Glu Gly
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Ser Gly Gly Arg Ile Thr Phe Asn Val Asp Leu Asn Ser Val Phe Leu
420 425 430

Arg Val Leu Asp Asp Glu Asp Ser Asp Asp Leu Glu Ala Pro Leu Met
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Leu Ser Ser His Leu Glu Glu Met Val Asp Pro Glu Asp Pro Asp Asn
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Val Gln Ser Asn His Leu Leu Ala Ser Gly Glu Gly Thr Gln Pro Thr
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Asn Phe Lys Asn Ile Leu Gln Trp Glu Ser Pro Ala Phe Ala Lys Gly
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Asn Leu Thr Phe Thr Ala Gln Tyr Leu Ser Tyr Arg Ile Phe Gln Asp
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Lys Cys Met Asn Thr Thr Leu Thr Glu Cys Asp Phe Ser Ser Leu Ser
 65 70 75 80

Lys Tyr Gly Asp His Thr Leu Arg Val Arg Ala Glu Phe Ala Asp Glu
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His Ser Asp Trp Val Asn Ile Thr Phe Cys Pro Val Asp Asp Thr Ile
 100 105 110

Ile Gly Pro Pro Gly Met Gln Val Glu Val Leu Ala Asp Ser Leu His
 115 120 125

Met Arg Phe Leu Ala Pro Lys Ile Glu Asn Glu Tyr Glu Thr Trp Thr
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Met Lys Asn Val Tyr Asn Ser Trp Thr Tyr Asn Val Gln Tyr Trp Lys

145	150	155	160
Asn Gly Thr Asp Glu Lys Phe Gln Ile Thr Pro Gln Tyr Asp Phe Glu	165	170	175
Val Leu Arg Asn Leu Glu Pro Trp Thr Thr Tyr Cys Val Gln Val Arg	180	185	190
Gly Phe Leu Pro Asp Arg Asn Lys Ala Gly Glu Trp Ser Glu Pro Val	195	200	205
Cys Glu Gln Thr Thr His Asp Glu Thr Val Pro Ser Trp Met Val Ala	210	215	220
Val Ile Leu Met Ala Ser Val Phe Met Val Cys Leu Ala Leu Leu Gly	225	230	235
Cys Phe Ser Leu Leu Trp Cys Val Tyr Lys Lys Thr Lys Tyr Ala Phe	245	250	255
Ser Pro Arg Asn Ser Leu Pro Gln His Leu Lys Glu Phe Leu Gly His	260	265	270
Pro His His Asn Thr Leu Leu Phe Phe Ser Phe Pro Leu Ser Asp Glu	275	280	285
Asn Asp Val Phe Asp Lys Leu Ser Val Ile Ala Glu Asp Ser Glu Ser	290	295	300
Gly Lys Gln Asn Pro Gly Asp Ser Cys Ser Leu Gly Thr Pro Pro Gly	305	310	315
Gln Gly Pro Gln Ser	325		

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Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
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Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
 65 70 75 80

Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
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Glu Pro Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
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Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Thr Lys Ile
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Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu Leu Val
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Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu Lys Asn
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Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe Ile Ile
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Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala His Arg
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Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys Val Val
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Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly
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Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys
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Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp
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Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val
100 105 110

Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg
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Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu
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Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys
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Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr
165 170 175

Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg
180 185 190

Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu
195 200 205

Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe Val Pro Gly
210 215 220

Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu
225 230 235 240

Lys Asp Gln Ser Ser Glu Phe Lys Ala Lys Ile Ile Phe Trp Tyr Val
245 250 255

Leu Pro Ile Ser Ile Thr Val Phe Leu Phe Ser Val Met Gly Tyr Ser
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Ile Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro Ala Asn Leu
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Ile Leu Ile Tyr Gly Asn Glu Phe Asp Lys Arg Phe Phe Val Pro Ala
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Glu Lys Ile Val Ile Asn Phe Ile Thr Leu Asn Ile Ser Asp Asp Ser
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Lys Ile Ser His Gln Asp Met Ser Leu Leu Gly Lys Ser Ser Asp Val
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Ser Ser Leu Asn Asp Pro Gln Pro Ser Gly Asn Leu Arg Pro Pro Gln
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Glu Glu Glu Glu Val Lys His Leu Gly Tyr Ala Ser His Leu Met Glu
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370 375 380

Gln Glu Ser Leu Ser Arg Thr Ile Pro Pro Asp Lys Thr Val Ile Glu
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Tyr Glu Tyr Asp Val Arg Thr Thr Asp Ile Cys Ala Gly Pro Glu Glu
 405 410 415

Gln Glu Leu Ser Leu Gln Glu Glu Val Ser Thr Gln Gly Thr Leu Leu
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Glu Ser Gln Ala Ala Leu Ala Val Leu Gly Pro Gln Thr Leu Gln Tyr
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Ser Tyr Thr Pro Gln Leu Gln Asp Leu Asp Pro Leu Ala Gln Glu His
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Thr Asp Ser Glu Glu Gly Pro Glu Glu Glu Pro Ser Thr Thr Leu Val
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Asp Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser Leu Ser Ser
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Phe Asp Gln Asp Ser Glu Gly Cys Glu Pro Ser Glu Gly Asp Gly Leu
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Gly Glu Glu Gly Leu Leu Ser Arg Leu Xaa Glu Glu Pro Ala Pro Asp
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 Thr Ser Arg Cys Arg Ser Asp Arg Gly Asp Ser Ala Ser Arg Val Ser
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 Gly Ala Ala Glu Arg Gly His Gly Ala Pro Val Leu Arg Ala Ser Gly
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ccc gct gct gcc cca ggg gcg ggc ctg cgg ctg gtg ggc gag gcc ttt 240
 Pro Ala Ala Ala Pro Gly Ala Gly Leu Arg Leu Val Gly Glu Ala Phe
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cac tgc cgg ctg cag ggt ccc cgc cgg gtg gac aag cgg acg ctg gtg 288
 His Cys Arg Leu Gln Gly Pro Arg Arg Val Asp Lys Arg Thr Leu Val
 85 90 95

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 Gly Ser Gly Leu Ser Leu Ala Ser Gly Arg Phe Thr Ala Pro Val Ser
 115 120 125

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 Gly Ile Phe Gln Phe Ser Ala Ser Leu His Val Asp His Ser Glu Leu
 130 135 140

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 Gln Gly Lys Ala Arg Leu Arg Ala Arg Asp Val Val Cys Val Leu Ile
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 Gly Leu Glu Ser Asn Ser Arg Val Phe Thr Leu Gln Val Gln Gly Leu
 180 185 190

ctg cag ctg cag gct gga cag tac gct tct gtg ttt gtg gac aat ggc 624
 Leu Gln Leu Gln Ala Gly Gln Tyr Ala Ser Val Phe Val Asp Asn Gly
 195 200 205

14

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Thr Ser Arg Cys Arg Ser Asp Arg Gly Asp Ser Ala Ser Arg Val Ser
 35 40 45

Gly Ala Ala Glu Arg Gly His Gly Ala Pro Val Leu Arg Ala Ser Gly
 50 55 60

Pro Ala Ala Ala Pro Gly Ala Gly Leu Arg Leu Val Gly Glu Ala Phe
 65 70 75 80

His Cys Arg Leu Gln Gly Pro Arg Arg Val Asp Lys Arg Thr Leu Val
 85 90 95

Glu Leu His Gly Phe Gln Ala Pro Ala Ala Gln Gly Ala Phe Leu Arg
 100 105 110

Gly Ser Gly Leu Ser Leu Ala Ser Gly Arg Phe Thr Ala Pro Val Ser
 115 120 125

Gly Ile Phe Gln Phe Ser Ala Ser Leu His Val Asp His Ser Glu Leu
 130 135 140

Gln Gly Lys Ala Arg Leu Arg Ala Arg Asp Val Val Cys Val Leu Ile
 145 150 155 160

16

gcg cgt gtg gat tcc ccc aat att acc acg tcc aac cgt gag gga ttc Ala Arg Val Asp Ser Pro Asn Ile Thr Thr Ser Asn Arg Glu Gly Phe 35 40 45	384
cca ggc tcc gtc aag ccc ccg gaa gcc tct gga cct gag ctc tca gat Pro Gly Ser Val Lys Pro Pro Glu Ala Ser Gly Pro Glu Leu Ser Asp 50 55 60	432
gcc cac atg acg tgg ttg aac ttt gtc cga cgg cca gat gat ggg tcc Ala His Met Thr Trp Leu Asn Phe Val Arg Arg Pro Asp Asp Gly Ser 65 70 75 80	480
ccc cca gga cct cct ggc cct cct ggt ccc cct ggc tcc cct ggt gtg Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Ser Pro Gly Val 85 90 95	528
ggc gtt acc cca gag gcc tta ctg cag gaa ttt cag gag ata ctg aaa Gly Val Thr Pro Glu Ala Leu Leu Gln Glu Phe Gln Glu Ile Leu Lys 100 105 110	576
gag gcc aca gaa ctt cga ttc tca ggg cta cca gac aca ttg tta ccc Glu Ala Thr Glu Leu Arg Phe Ser Gly Leu Pro Asp Thr Leu Leu Pro 115 120 125	624
cag gaa ccc agc caa cgg ctg gtg gtt gag gcc ttc tac tgc cgt ttg Gln Glu Pro Ser Gln Arg Leu Val Val Glu Ala Phe Tyr Cys Arg Leu 130 135 140	672
aaa ggc cct gtg ctg gtg gac aag aag act ctg gtg gaa ctg caa gga Lys Gly Pro Val Leu Val Asp Lys Lys Thr Leu Val Glu Leu Gln Gly 145 150 155 160	720
ttc caa gct cct act act cag ggc gcc ttc ctg cgg gga tct ggc ctg Phe Gln Ala Pro Thr Thr Gln Gly Ala Phe Leu Arg Gly Ser Gly Leu 165 170 175	768
agc ctg tcc ttg ggc cga ttc aca gcc cca gtc tct gcc atc ttc cag Ser Leu Ser Leu Gly Arg Phe Thr Ala Pro Val Ser Ala Ile Phe Gln 180 185 190	816
ttt tct gcc agc ctg cac gtg gac cac agt gaa ctg cag ggc aga ggc Phe Ser Ala Ser Leu His Val Asp His Ser Glu Leu Gln Gly Arg Gly 195 200 205	864
cgg ttg cgt acc cgg gat atg gtc cgt gtt ctc atc tgt att gag tcc Arg Leu Arg Thr Arg Asp Met Val Arg Val Leu Ile Cys Ile Glu Ser 210 215 220	912
ttg tgt cat cgt cat acg tcc ctg gag gct gta tca ggt ctg gag agc Leu Cys His Arg His Thr Ser Leu Glu Ala Val Ser Gly Leu Glu Ser 225 230 235 240	960
aac agc agg gtc ttc aca gtg cag gtt cag ggg ctg ctg cat cta cag Asn Ser Arg Val Phe Thr Val Gln Val Gln Gly Leu Leu His Leu Gln 245 250 255	1008
tct gga cag tat gtc tct gtg ttc gtg gac aac agt tct ggg gca gtc Ser Gly Gln Tyr Val Ser Val Phe Val Asp Asn Ser Ser Gly Ala Val 260 265 270	1056

17

ctc acc atc cag aac act tcc agc ttc tcg gga atg ctt ttg ggt acc 1104
 Leu Thr Ile Gln Asn Thr Ser Ser Phe Ser Gly Met Leu Leu Gly Thr
 275 280 285

tagcggagct gaagaaacga ttgtggattg aggaaccaac accttgcttc ttagaggagc 1164

tgaaaaggac tactcactcc ccttttaata gttttcatag caataaagaa ctccaaactt 1224

cttcatct 1232

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<211> 288

<212> PRT

<213> Mus musculus

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Ala Arg Val Asp Ser Pro Asn Ile Thr Thr Ser Asn Arg Glu Gly Phe
 35 40 45

Pro Gly Ser Val Lys Pro Pro Glu Ala Ser Gly Pro Glu Leu Ser Asp
 50 55 60

Ala His Met Thr Trp Leu Asn Phe Val Arg Arg Pro Asp Asp Gly Ser
 65 70 75 80

Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Ser Pro Gly Val
 85 90 95

Gly Val Thr Pro Glu Ala Leu Leu Gln Glu Phe Gln Glu Ile Leu Lys
 100 105 110

Glu Ala Thr Glu Leu Arg Phe Ser Gly Leu Pro Asp Thr Leu Leu Pro
 115 120 125

Gln Glu Pro Ser Gln Arg Leu Val Val Glu Ala Phe Tyr Cys Arg Leu
 130 135 140

18

Lys Gly Pro Val Leu Val Asp Lys Lys Thr Leu Val Glu Leu Gln Gly
 145 150 155 160

Phe Gln Ala Pro Thr Thr Gln Gly Ala Phe Leu Arg Gly Ser Gly Leu
 165 170 175

Ser Leu Ser Leu Gly Arg Phe Thr Ala Pro Val Ser Ala Ile Phe Gln
 180 185 190

Phe Ser Ala Ser Leu His Val Asp His Ser Glu Leu Gln Gly Arg Gly
 195 200 205

Arg Leu Arg Thr Arg Asp Met Val Arg Val Leu Ile Cys Ile Glu Ser
 210 215 220

Leu Cys His Arg His Thr Ser Leu Glu Ala Val Ser Gly Leu Glu Ser
 225 230 235 240

Asn Ser Arg Val Phe Thr Val Gln Val Gln Gly Leu Leu His Leu Gln
 245 250 255

Ser Gly Gln Tyr Val Ser Val Phe Val Asp Asn Ser Ser Gly Ala Val
 260 265 270

Leu Thr Ile Gln Asn Thr Ser Ser Phe Ser Gly Met Leu Leu Gly Thr
 275 280 285

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<211> 477

<212> DNA

<213> Homo sapiens

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48

19

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 1 5 10 15

ttg gtg gag cgg cgc gcg ctg cac gag ctt ggc gtc tac tac ctg ccc 96
 Leu Val Glu Arg Arg Ala Leu His Glu Leu Gly Val Tyr Tyr Leu Pro
 20 25 30

gac gcc gag ggt gcc ttc cgc cgc ggc ccg ggc ctg aac ttg acc agc 144
 Asp Ala Glu Gly Ala Phe Arg Arg Gly Pro Gly Leu Asn Leu Thr Ser
 35 40 45

ggc cag tac agg gcg ccc gtg gct ggc ttc tac gct ctc gcc gcc acg 192
 Gly Gln Tyr Arg Ala Pro Val Ala Gly Phe Tyr Ala Leu Ala Ala Thr
 50 55 60

ctg cac gtg gcg ctc ggg gag ccg ccg agg agg ggg ccg ccg cgc ccc 240
 Leu His Val Ala Leu Gly Glu Pro Pro Arg Arg Gly Pro Pro Arg Pro
 65 70 75 80

cgg gac cac ctg cgc ctg ctc atc tgc atc cag tcc cgg tgc cag cgc 288
 Arg Asp His Leu Arg Leu Leu Ile Cys Ile Gln Ser Arg Cys Gln Arg
 85 90 95

aac acg tcc ctg gag gcc atc atg ggc ctg gag agc agc agt gag ctc 336
 Asn Thr Ser Leu Glu Ala Ile Met Gly Leu Glu Ser Ser Ser Glu Leu
 100 105 110

ttc acc atc tct gtg aat ggc gtc ctg tac ctg cag atg ggg cag tgg 384
 Phe Thr Ile Ser Val Asn Gly Val Leu Tyr Leu Gln Met Gly Gln Trp
 115 120 125

acc tcc tgg gcg tgt gag cgg cca cca cag gcc ctt cct ctc agg ggc 432
 Thr Ser Trp Ala Cys Glu Arg Pro Pro Gln Ala Leu Pro Leu Arg Gly
 130 135 140

aaa tgg agc aca gat cta gac aat gtg tgg aca gtg tca gag tag 477
 Lys Trp Ser Thr Asp Leu Asp Asn Val Trp Thr Val Ser Glu
 145 150 155

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<211> 158

<212> PRT

<213> Homo sapiens

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Ala Pro Arg Val Glu Ala Ala Phe Leu Cys Arg Leu Arg Arg Asp Ala
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Leu Val Glu Arg Arg Ala Leu His Glu Leu Gly Val Tyr Tyr Leu Pro
 20 25 30

20

Asp Ala Glu Gly Ala Phe Arg Arg Gly Pro Gly Leu Asn Leu Thr Ser
 35 40 45

Gly Gln Tyr Arg Ala Pro Val Ala Gly Phe Tyr Ala Leu Ala Ala Thr
 50 55 60

Leu His Val Ala Leu Gly Glu Pro Pro Arg Arg Gly Pro Pro Arg Pro
 65 70 75 80

Arg Asp His Leu Arg Leu Leu Ile Cys Ile Gln Ser Arg Cys Gln Arg
 85 90 95

Asn Thr Ser Leu Glu Ala Ile Met Gly Leu Glu Ser Ser Ser Glu Leu
 100 105 110

Phe Thr Ile Ser Val Asn Gly Val Leu Tyr Leu Gln Met Gly Gln Trp
 115 120 125

Thr Ser Trp Ala Cys Glu Arg Pro Pro Gln Ala Leu Pro Leu Arg Gly
 130 135 140

Lys Trp Ser Thr Asp Leu Asp Asn Val Trp Thr Val Ser Glu
 145 150 155

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<222> (143) .. (2677)

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 gtggactgca gaggagaggg attcagtctt ctctgatgt gtttgccctgt aggtacctga 120
 gttgacaccg aagctcctaa ag atg ctg agc ggc gtt tgg ttc ctc agt gtg 172

21

	Met	Leu	Ser	Gly	Val	Trp	Phe	Leu	Ser	Val	
	1				5					10	
tta acc gtg gcc ggg atc tta cag aca gag agt cgc aaa act gcc aaa											220
Leu Thr Val Ala Gly Ile Leu Gln Thr Glu Ser Arg Lys Thr Ala Lys											
				15				20		25	
gac att tgc aag atc cgc tgt ctg tgc gaa gaa aag gaa aac gta ctg											268
Asp Ile Cys Lys Ile Arg Cys Leu Cys Glu Glu Lys Glu Asn Val Leu											
			30					35		40	
aat atc aac tgt gag aac aaa gga ttt aca aca gtt agc ctg ctc cag											316
Asn Ile Asn Cys Glu Asn Lys Gly Phe Thr Thr Val Ser Leu Leu Gln											
			45					50		55	
ccc ccc cag tat cga atc tat cag ctt ttt ctc aat gga aac ctc ttg											364
Pro Pro Gln Tyr Arg Ile Tyr Gln Leu Phe Leu Asn Gly Asn Leu Leu											
			60					65		70	
aca aga ctg tat cca aac gaa ttt gtc aat tac tcc aac gcg gtg act											412
Thr Arg Leu Tyr Pro Asn Glu Phe Val Asn Tyr Ser Asn Ala Val Thr											
			75					80		85	90
ctt cac cta ggt aac aac ggg tta cag gag atc cga acg ggg gca ttc											460
Leu His Leu Gly Asn Asn Gly Leu Gln Glu Ile Arg Thr Gly Ala Phe											
				95				100		105	
agt ggc ctg aaa act ctc aaa aga ctg cat ctc aac aac aac aag ctt											508
Ser Gly Leu Lys Thr Leu Lys Arg Leu His Leu Asn Asn Asn Lys Leu											
			110					115		120	
gag ata ttg agg gag gac acc ttc cta ggc ctg gag agc ctg gag tat											556
Glu Ile Leu Arg Glu Asp Thr Phe Leu Gly Leu Glu Ser Leu Glu Tyr											
			125					130		135	
ctc cag gcc gac tac aat tac atc agt gcc atc gag gct ggg gca ttc											604
Leu Gln Ala Asp Tyr Asn Tyr Ile Ser Ala Ile Glu Ala Gly Ala Phe											
			140					145		150	
agc aaa ctt aac aag ctc aaa gtg ctc atc ctg aat gac aac ctt ctg											652
Ser Lys Leu Asn Lys Leu Lys Val Leu Ile Leu Asn Asp Asn Leu Leu											
			155					160		165	170
ctt tca ctg ccc agc aat gtg ttc cgc ttt gtc ctg ctg acc cac tta											700
Leu Ser Leu Pro Ser Asn Val Phe Arg Phe Val Leu Leu Thr His Leu											
				175				180		185	
gac ctc agg ggg aat agg cta aaa gta atg cct ttt gct ggc gtc ctt											748
Asp Leu Arg Gly Asn Arg Leu Lys Val Met Pro Phe Ala Gly Val Leu											
			190					195		200	
gaa cat att gga ggg atc atg gag att cag ctg gag gaa aat cca tgg											796
Glu His Ile Gly Gly Ile Met Glu Ile Gln Leu Glu Glu Asn Pro Trp											
			205					210		215	
aat tgc act tgt gac tta ctt cct ctc aag gcc tgg cta gac acc ata											844
Asn Cys Thr Cys Asp Leu Leu Pro Leu Lys Ala Trp Leu Asp Thr Ile											
			220					225		230	

22

act gtt ttt gtg gga gag att gtc tgt gag act ccc ttt agg ttg cat	892
Thr Val Phe Val Gly Glu Ile Val Cys Glu Thr Pro Phe Arg Leu His	
235 240 245 250	
ggg aaa gac gtg acc cag ctg acc agg caa gac ctc tgt ccc aga aaa	940
Gly Lys Asp Val Thr Gln Leu Thr Arg Gln Asp Leu Cys Pro Arg Lys	
255 260 265	
agt gcc agt gat tcc agt cag agg ggc agc cat gct gac acc cac gtc	988
Ser Ala Ser Asp Ser Ser Gln Arg Gly Ser His Ala Asp Thr His Val	
270 275 280	
caa agg ctg tca cct aca atg aat cct gct ctc aac cca acc agg gct	1036
Gln Arg Leu Ser Pro Thr Met Asn Pro Ala Leu Asn Pro Thr Arg Ala	
285 290 295	
ccg aaa gcc agc cgg ccg ccc aaa atg aga aat cgt cca act ccc cga	1084
Pro Lys Ala Ser Arg Pro Pro Lys Met Arg Asn Arg Pro Thr Pro Arg	
300 305 310	
gtg act gtg tca aag gac agg caa agt ttt gga ccc atc atg gtg tac	1132
Val Thr Val Ser Lys Asp Arg Gln Ser Phe Gly Pro Ile Met Val Tyr	
315 320 325 330	
cag acc aag tct cct gtg cct ctc acc tgt ccc agc agc tgt gtc tgc	1180
Gln Thr Lys Ser Pro Val Pro Leu Thr Cys Pro Ser Ser Cys Val Cys	
335 340 345	
acc tct cag agc tca gac aat ggt ctg aat gta aac tgc caa gaa agg	1228
Thr Ser Gln Ser Ser Asp Asn Gly Leu Asn Val Asn Cys Gln Glu Arg	
350 355 360	
aag ttc act aat atc tct gac ctg cag ccc aaa ccg acc agt cca aag	1276
Lys Phe Thr Asn Ile Ser Asp Leu Gln Pro Lys Pro Thr Ser Pro Lys	
365 370 375	
aaa ctc tac cta aca ggg aac tat ctt caa act gtc tat aag aat gac	1324
Lys Leu Tyr Leu Thr Gly Asn Tyr Leu Gln Thr Val Tyr Lys Asn Asp	
380 385 390	
ctc tta gaa tac agt tct ttg gac tta ctg cac tta gga aac aac agg	1372
Leu Leu Glu Tyr Ser Ser Leu Asp Leu Leu His Leu Gly Asn Asn Arg	
395 400 405 410	
att gca gtc att cag gaa ggt gcc ttt aca aac ctg acc agt tta cgc	1420
Ile Ala Val Ile Gln Glu Gly Ala Phe Thr Asn Leu Thr Ser Leu Arg	
415 420 425	
aga ctt tat ctg aat ggc aat tac ctt gaa gtg ctg tac cct tct atg	1468
Arg Leu Tyr Leu Asn Gly Asn Tyr Leu Glu Val Leu Tyr Pro Ser Met	
430 435 440	
ttt gat gga ctg cag agc ttg caa tat ctc tat tta gag tat aat gtc	1516
Phe Asp Gly Leu Gln Ser Leu Gln Tyr Leu Tyr Leu Glu Tyr Asn Val	
445 450 455	
att aag gaa att aag cct ctg acc ttt gat gct ttg att aac cta cag	1564
Ile Lys Glu Ile Lys Pro Leu Thr Phe Asp Ala Leu Ile Asn Leu Gln	
460 465 470	

cta ctg ttt ctg aac aac aac ctt ctt cgg tcc tta cct gat aat ata Leu Leu Phe Leu Asn Asn Asn Leu Leu Arg Ser Leu Pro Asp Asn Ile 475 480 485 490	1612
ttt ggg ggg acg gcc cta acc agg ctg aat ctg aga aac aac cat ttt Phe Gly Gly Thr Ala Leu Thr Arg Leu Asn Leu Arg Asn Asn His Phe 495 500 505	1660
tct cac ctg ccc gtg aaa ggg gtt ctg gat cag ctc ccg gct ttc atc Ser His Leu Pro Val Lys Gly Val Leu Asp Gln Leu Pro Ala Phe Ile 510 515 520	1708
cag ata gat ctg cag gag aac ccc tgg gac tgt acc tgt gac atc atg Gln Ile Asp Leu Gln Glu Asn Pro Trp Asp Cys Thr Cys Asp Ile Met 525 530 535	1756
ggg ctg aaa gac tgg aca gaa cat gcc aat tcc cct gtc atc att aat Gly Leu Lys Asp Trp Thr Glu His Ala Asn Ser Pro Val Ile Ile Asn 540 545 550	1804
gag gtg act tgc gaa tct cct gct aag cat gca ggg gag ata cta aaa Glu Val Thr Cys Glu Ser Pro Ala Lys His Ala Gly Glu Ile Leu Lys 555 560 565 570	1852
ttt ctg ggg agg gag gct atc tgt cca gac agc cca aac ttg tca gat Phe Leu Gly Arg Glu Ala Ile Cys Pro Asp Ser Pro Asn Leu Ser Asp 575 580 585	1900
gga acc gtc ttg tca atg aat cac aat aca gac aca cct cgg tcg ctt Gly Thr Val Leu Ser Met Asn His Asn Thr Asp Thr Pro Arg Ser Leu 590 595 600	1948
agt gtg tct cct agt tcc tat cct gaa cta cac act gaa gtt cca ctg Ser Val Ser Pro Ser Ser Tyr Pro Glu Leu His Thr Glu Val Pro Leu 605 610 615	1996
tct gtc tta att ctg gga ttg ctt gtt gtt ttc atc tta tct gtc tgt Ser Val Leu Ile Leu Gly Leu Leu Val Val Phe Ile Leu Ser Val Cys 620 625 630	2044
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ccg agc gtt ccc agg aat acc aac aac tta gac gta agc tcc ttt caa Pro Ser Val Pro Arg Asn Thr Asn Asn Leu Asp Val Ser Ser Phe Gln 655 660 665	2140
tta cag tat ggg tct tac aac act gag act cac gat aaa aca gac ggc Leu Gln Tyr Gly Ser Tyr Asn Thr Glu Thr His Asp Lys Thr Asp Gly 670 675 680	2188
cat gtc tac aac tat atc ccc cca cct gtg ggt cag atg tgc caa aac His Val Tyr Asn Tyr Ile Pro Pro Pro Val Gly Gln Met Cys Gln Asn 685 690 695	2236
ccc atc tac atg cag aag gaa gga gac cca gta gcc tat tac cga aac Pro Ile Tyr Met Gln Lys Glu Gly Asp Pro Val Ala Tyr Tyr Arg Asn 695 700 705	2284

700	705	710	
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gcc aca cca aga gag cct gag ctg ctg tat caa aat att gct gag cga Ala Thr Pro Arg Glu Pro Glu Leu Leu Tyr Gln Asn Ile Ala Glu Arg 750 755 760			2428
gtc aag gaa ctt ccc agc gca ggc cta gtc cac tat aac ttt tgt acc Val Lys Glu Leu Pro Ser Ala Gly Leu Val His Tyr Asn Phe Cys Thr 765 770 775			2476
tta cct aaa agg cag ttt gcc cct tcc tat gaa tct cga cgc caa aac Leu Pro Lys Arg Gln Phe Ala Pro Ser Tyr Glu Ser Arg Arg Gln Asn 780 785 790			2524
caa gac aga atc aat aaa acc gtt tta tat gga act ccc agg aaa tgc Gln Asp Arg Ile Asn Lys Thr Val Leu Tyr Gly Thr Pro Arg Lys Cys 795 800 805 810			2572
ttt gtg ggg cag tca aaa ccc aac cac cct tta ctg caa gct aag ccg Phe Val Gly Gln Ser Lys Pro Asn His Pro Leu Leu Gln Ala Lys Pro 815 820 825			2620
caa tca gaa ccg gac tac ctc gaa gtt ctg gaa aaa caa act gca atc Gln Ser Glu Pro Asp Tyr Leu Glu Val Leu Glu Lys Gln Thr Ala Ile 830 835 840			2668
agt cag ctg tgaagggaaa tcatttacaa ccctaaggca tcagaggatg Ser Gln Leu 845			2717
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25

<212> PRT

<213> Homo sapiens

<400> 15

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 20 25 30

Cys Leu Cys Glu Glu Lys Glu Asn Val Leu Asn Ile Asn Cys Glu Asn
 35 40 45

Lys Gly Phe Thr Thr Val Ser Leu Leu Gln Pro Pro Gln Tyr Arg Ile
 50 55 60

Tyr Gln Leu Phe Leu Asn Gly Asn Leu Leu Thr Arg Leu Tyr Pro Asn
 65 70 75 80

Glu Phe Val Asn Tyr Ser Asn Ala Val Thr Leu His Leu Gly Asn Asn
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Gly Leu Gln Glu Ile Arg Thr Gly Ala Phe Ser Gly Leu Lys Thr Leu
 100 105 110

Lys Arg Leu His Leu Asn Asn Asn Lys Leu Glu Ile Leu Arg Glu Asp
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Thr Phe Leu Gly Leu Glu Ser Leu Glu Tyr Leu Gln Ala Asp Tyr Asn
 130 135 140

Tyr Ile Ser Ala Ile Glu Ala Gly Ala Phe Ser Lys Leu Asn Lys Leu
 145 150 155 160

Lys Val Leu Ile Leu Asn Asp Asn Leu Leu Leu Ser Leu Pro Ser Asn
 165 170 175

Val Phe Arg Ph Val Leu Leu Thr His Leu Asp Leu Arg Gly Asn Arg
 180 185 190

Leu Lys Val Met Pro Phe Ala Gly Val Leu Glu His Ile Gly Gly Ile
 195 200 205

Met Glu Ile Gln Leu Glu Glu Asn Pro Trp Asn Cys Thr Cys Asp Leu
 210 215 220

Leu Pro Leu Lys Ala Trp Leu Asp Thr Ile Thr Val Phe Val Gly Glu
 225 230 235 240

Ile Val Cys Glu Thr Pro Phe Arg Leu His Gly Lys Asp Val Thr Gln
 245 250 255

Leu Thr Arg Gln Asp Leu Cys Pro Arg Lys Ser Ala Ser Asp Ser Ser
 260 265 270

Gln Arg Gly Ser His Ala Asp Thr His Val Gln Arg Leu Ser Pro Thr
 275 280 285

Met Asn Pro Ala Leu Asn Pro Thr Arg Ala Pro Lys Ala Ser Arg Pro
 290 295 300

Pro Lys Met Arg Asn Arg Pro Thr Pro Arg Val Thr Val Ser Lys Asp
 305 310 315 320

Arg Gln Ser Phe Gly Pro Ile Met Val Tyr Gln Thr Lys Ser Pro Val
 325 330 335

Pro Leu Thr Cys Pro Ser Ser Cys Val Cys Thr Ser Gln Ser Ser Asp
 340 345 350

Asn Gly Leu Asn Val Asn Cys Gln Glu Arg Lys Phe Thr Asn Ile Ser
 355 360 365

Asp Leu Gln Pro Lys Pro Thr Ser Pro Lys Lys Leu Tyr Leu Thr Gly
 370 375 380

Asn Tyr Leu Gln Thr Val Tyr Lys Asn Asp Leu Leu Glu Tyr Ser Ser
 385 390 395 400

Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ala Val Ile Gln Glu
 405 410 415

Gly Ala Phe Thr Asn Leu Thr Ser Leu Arg Arg Leu Tyr Leu Asn Gly
 420 425 430

Asn Tyr Leu Glu Val Leu Tyr Pro Ser Met Phe Asp Gly Leu Gln Ser
 435 440 445

Leu Gln Tyr Leu Tyr Leu Glu Tyr Asn Val Ile Lys Glu Ile Lys Pro
 450 455 460

Leu Thr Phe Asp Ala Leu Ile Asn Leu Gln Leu Leu Phe Leu Asn Asn
 465 470 475 480

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Thr Arg Leu Asn Leu Arg Asn Asn His Phe Ser His Leu Pro Val Lys
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Gly Val Leu Asp Gln Leu Pro Ala Phe Ile Gln Ile Asp Leu Gln Glu
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Asn Pro Trp Asp Cys Thr Cys Asp Ile Met Gly Leu Lys Asp Trp Thr
 530 535 540

Glu His Ala Asn Ser Pro Val Ile Ile Asn Glu Val Thr Cys Glu Ser
 545 550 555 560

Pro Ala Lys His Ala Gly Glu Ile Leu Lys Phe Leu Gly Arg Glu Ala
 565 570 575

Ile Cys Pro Asp Ser Pro Asn Leu Ser Asp Gly Thr Val Leu Ser Met
 580 585 590

Asn His Asn Thr Asp Thr Pro Arg Ser Leu Ser Val Ser Pro Ser Ser
 595 600 605

Tyr Pro Glu Leu His Thr Glu Val Pro Leu Ser Val Leu Ile Leu Gly
 610 615 620

Leu Leu Val Val Phe Ile Leu Ser Val Cys Phe Gly Ala Gly Leu Phe
 625 630 635 640

Val Phe Val Leu Lys Arg Arg Lys Gly Val Pro Ser Val Pro Arg Asn
 645 650 655

Thr Asn Asn Leu Asp Val Ser Ser Phe Gln Leu Gln Tyr Gly Ser Tyr
 660 665 670

Asn Thr Glu Thr His Asp Lys Thr Asp Gly His Val Tyr Asn Tyr Ile

28

675	680	685
Pro Pro Pro Val Gly Gln Met Cys Gln Asn Pro Ile Tyr Met Gln Lys		
690	695	700
Glu Gly Asp Pro Val Ala Tyr Tyr Arg Asn Leu Gln Glu Phe Ser Tyr		
705	710	715
Ser Asn Leu Glu Glu Lys Lys Glu Glu Pro Ala Thr Pro Ala Tyr Thr		
	725	730
Ile Ser Ala Thr Glu Leu Leu Glu Lys Gln Ala Thr Pro Arg Glu Pro		
	740	745
Glu Leu Leu Tyr Gln Asn Ile Ala Glu Arg Val Lys Glu Leu Pro Ser		
	755	760
Ala Gly Leu Val His Tyr Asn Phe Cys Thr Leu Pro Lys Arg Gln Phe		
	770	775
Ala Pro Ser Tyr Glu Ser Arg Arg Gln Asn Gln Asp Arg Ile Asn Lys		
	785	790
Thr Val Leu Tyr Gly Thr Pro Arg Lys Cys Phe Val Gly Gln Ser Lys		
	805	810
Pro Asn His Pro Leu Leu Gln Ala Lys Pro Gln Ser Glu Pro Asp Tyr		
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taccccgaac tacacactga agttccactc tccgttttaa ttttaggatt gcttgtgggt		180

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tatgggtctt acaacaccga gactaatgat aaagctgatg gccacgtcta taactacatt      360
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<212> PRT

<213> Mus musculus

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          20          25          30

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Ser Leu Ser Val Ser Pro Ser Ser Tyr Pro Glu Leu His Thr Glu Val
          35          40          45

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Pro Leu Ser Val Leu Ile Leu Gly Leu Leu Val Val Phe Ile Leu Ser
          50          55          60

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Val Cys Phe Gly Ala Gly Leu Phe Val Phe Val Leu Lys Arg Arg Lys
          65          70          75          80

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Gly Val Pro Asn Val Pro Arg Asn Ala Thr Asn Leu Asp Val Ser Ser
          85          90          95

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Phe Gln Leu Gln Tyr Gly Ser Tyr Asn Thr Glu Thr Asn Asp Lys Ala
          100          105          110

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Asp Gly His Val Tyr Asn Tyr Ile Pro Pro Pro Val Gly Gln Met Cys
          115          120          125

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Gln Asn Pro Ile Tyr Met Gln Lys Glu Gly Asp Pro Val Ala Tyr Tyr
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 Met Leu Gln Thr Leu Ala Phe Ala
 1 5
 gta aca tct ctc gtc ctt tcg tgt gca gaa acc atc gat tat tac ggg 160
 Val Thr Ser Leu Val Leu Ser Cys Ala Glu Thr Ile Asp Tyr Tyr Gly
 10 15 20
 gaa atc tgt gac aat gca tgt cct tgt gag gaa aag gac ggc att tta 208
 Glu Ile Cys Asp Asn Ala Cys Pro Cys Glu Glu Lys Asp Gly Ile Leu
 25 30 35 40
 act gtg agc tgt gaa aac cgg ggg atc atc agt ctc tct gaa att agc 256
 Thr Val Ser Cys Glu Asn Arg Gly Ile Ile Ser Leu Ser Glu Ile Ser
 45 50 55
 cct ccc cgt ttc cca atc tac cac ctc ttg ttg tcc gga aac ctt ttg 304
 Pro Pro Arg Phe Pro Ile Tyr His Leu Leu Leu Ser Gly Asn Leu Leu
 60 65 70
 aac cgt ctc tat ccc aat gag ttt gtc aat tac act ggg gct tca att 352
 Asn Arg Leu Tyr Pro Asn Glu Phe Val Asn Tyr Thr Gly Ala Ser Ile
 75 80 85
 ttg cat cta ggt agc aat gtt atc cag gac att gag acc ggg gct ttc 400
 Leu His Leu Gly Ser Asn Val Ile Gln Asp Ile Glu Thr Gly Ala Phe
 90 95 100
 cat ggg cta cgg ggt ttg agg aga ttg cat cta aac aat aat aaa ctg 448
 His Gly Leu Arg Gly Leu Arg Arg Leu His Leu Asn Asn Asn Lys Leu
 105 110 115 120

gaa ctt ctg cga gat gat acc ttc ctt ggc ttg gag aac ctg gag tac	496
Glu Leu Leu Arg Asp Asp Thr Phe Leu Gly Leu Glu Asn Leu Glu Tyr	
125 130 135	
cta cag gtc gat tac aac tac atc agc gtc att gaa ccc aat gct ttt	544
Leu Gln Val Asp Tyr Asn Tyr Ile Ser Val Ile Glu Pro Asn Ala Phe	
140 145 150	
ggg aaa ctg cat ttg ttg cag gtg ctt atc ctc aat gac aat ctt ttg	592
Gly Lys Leu His Leu Leu Gln Val Leu Ile Leu Asn Asp Asn Leu Leu	
155 160 165	
tcc agt tta ccc aac aat ctt ttc cgt ttt gtg ccc tta acg cac ttg	640
Ser Ser Leu Pro Asn Asn Leu Phe Arg Phe Val Pro Leu Thr His Leu	
170 175 180	
gac ctc cgg ggg aac cgg ctg aaa ctt ctg ccc tac gtg ggg ctc ttg	688
Asp Leu Arg Gly Asn Arg Leu Lys Leu Leu Pro Tyr Val Gly Leu Leu	
185 190 195 200	
cag cac atg gat aaa gtt gtg gag cta cag ctg gag gaa aac cct tgg	736
Gln His Met Asp Lys Val Val Glu Leu Gln Leu Glu Glu Asn Pro Trp	
205 210 215	
aat tgt tct tgt gag ctg atc tct cta aag gat tgg ttg gac agc atc	784
Asn Cys Ser Cys Glu Leu Ile Ser Leu Lys Asp Trp Leu Asp Ser Ile	
220 225 230	
tcc tat tca gcc ctg gtg ggg gat gta gtt tgt gag acc ccc ttc cgc	832
Ser Tyr Ser Ala Leu Val Gly Asp Val Val Cys Glu Thr Pro Phe Arg	
235 240 245	
tta cac gga agg gac ttg gac gag gta tcc aag cag gaa ctt tgc cca	880
Leu His Gly Arg Asp Leu Asp Glu Val Ser Lys Gln Glu Leu Cys Pro	
250 255 260	
agg aga ctt att tct gac tac gag atg agg ccg cag acg cct ttg agc	928
Arg Arg Leu Ile Ser Asp Tyr Glu Met Arg Pro Gln Thr Pro Leu Ser	
265 270 275 280	
acc acg ggg tat tta cac acc acc ccg gcg tca gtg aat tct gtg gcc	976
Thr Thr Gly Tyr Leu His Thr Thr Pro Ala Ser Val Asn Ser Val Ala	
285 290 295	
act tct tcc tct gct gtt tac aaa ccc cct ttg aag ccc cct aag ggg	1024
Thr Ser Ser Ser Ala Val Tyr Lys Pro Pro Leu Lys Pro Pro Lys Gly	
300 305 310	
act cgc caa ccc aac aag ccc agg gtg cgc ccc acc tct cgg cag ccc	1072
Thr Arg Gln Pro Asn Lys Pro Arg Val Arg Pro Thr Ser Arg Gln Pro	
315 320 325	
tct aag gac ttg ggc tac agc aac tat ggc ccc agc atc gcc tat cag	1120
Ser Lys Asp Leu Gly Tyr Ser Asn Tyr Gly Pro Ser Ile Ala Tyr Gln	
330 335 340	
acc aaa tcc ccg gtg cct ttg gag tgt ccc acc gcg tgc tct tgc aac	1168
Thr Lys Ser Pro Val Pro Leu Glu Cys Pro Thr Ala Cys Ser Cys Asn	

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ctg cag atc tct gat	ctg ggc ctc aac gta	aac tgc cag gag cga aag		1216
Leu Gln Ile Ser Asp	Leu Gly Leu Asn Val	Asn Cys Gln Glu Arg Lys		
	365	370	375	
atc gag agc atc gct	gaa ctg cag ccc aag	ccc tac aat ccc aag aaa		1264
Ile Glu Ser Ile Ala	Glu Leu Gln Pro Lys	Pro Tyr Asn Pro Lys Lys		
	380	385	390	
atg tat ctg aca gag	aac tac atc gct gtc	gtg cgc agg aca gac ttc		1312
Met Tyr Leu Thr Glu	Asn Tyr Ile Ala Val	Val Arg Arg Thr Asp Phe		
	395	400	405	
ctg gag gcc acg ggg	ctg gac ctc ctg cac	ctg ggg aat aac cgc atc		1360
Leu Glu Ala Thr Gly	Leu Asp Leu Leu His	Leu Gly Asn Asn Arg Ile		
	410	415	420	
tcg atg atc cag gac	cgc gct ttc ggg gat	ctc acc aac ctg agg cgc		1408
Ser Met Ile Gln Asp	Arg Ala Phe Gly Asp	Leu Thr Asn Leu Arg Arg		
	425	430	435	440
ctc tac ctg aat ggc	aac agg atc gag agg	ctg agc ccg gag tta ttc		1456
Leu Tyr Leu Asn Gly	Asn Arg Ile Glu Arg	Leu Ser Pro Glu Leu Phe		
	445	450	455	
tat ggc ctg cag agc	ctg cag tat ctc ttc	ctc cag tac aat ctc atc		1504
Tyr Gly Leu Gln Ser	Leu Gln Tyr Leu Phe	Leu Gln Tyr Asn Leu Ile		
	460	465	470	
cgc gag att cag tct	gga act ttt gac ccg	gtc cca aac ctc cag ctg		1552
Arg Glu Ile Gln Ser	Gly Thr Phe Asp Pro	Val Pro Asn Leu Gln Leu		
	475	480	485	
cta ttc ttg aat aac	aac ctc ctg cag gcc	atg ccc tca ggc gtc ttc		1600
Leu Phe Leu Asn Asn	Asn Leu Gln Ala Met	Pro Ser Gly Val Phe		
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tct ggc ttg acc ctc	ctc agg cta aac ctg	agg agt aac cac ttc acc		1648
Ser Gly Leu Thr Leu	Leu Arg Leu Asn Leu	Arg Ser Asn His Phe Thr		
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tcc ttg cca gtg agt	gga gtt ttg gac cag	ctg aag tca ctc atc caa		1696
Ser Leu Pro Val Ser	Gly Val Leu Asp Gln	Leu Lys Ser Leu Ile Gln		
	525	530	535	
atc gac ctg cat gac	aat cct tgg gat tgt	acc tgt gac att gtg ggc		1744
Ile Asp Leu His Asp	Asn Pro Trp Asp Cys	Thr Cys Asp Ile Val Gly		
	540	545	550	
atg aag ctg tgg gtg	gag cag ctc aaa gtg	ggc gtc cta gtg gac gag		1792
Met Lys Leu Trp Val	Glu Gln Leu Lys Val	Gly Val Leu Val Asp Glu		
	555	560	565	
gtg atc tgt aag gcg	ccc aaa aaa ttc gct	gag acc gac atg cgc tcc		1840
Val Ile Cys Lys Ala	Pro Lys Lys Phe Ala	Glu Thr Asp Met Arg Ser		
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att aag tcg gag ctg	ctg tgc cct gac tat	tca gat gta gta gtt tcc		1888

Ile Lys Ser Glu Leu Leu Cys Pro Asp Tyr Ser Asp Val Val Val Ser	
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acg ccc aca ccc tcc tct atc cag gtc cct gcg agg acc agc gcc gtg	1936
Thr Pro Thr Pro Ser Ser Ile Gln Val Pro Ala Arg Thr Ser Ala Val	
605 610 615	
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620 625 630	
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Ala Gly Gly Gly Ala Ser Ser Val Pro Leu Ser Val Leu Ile Leu Ser	
635 640 645	
ctc ctg ctg gtt ttc atc atg tcc gtc ttc gtg gcc gcc ggg ctc ttc	2080
Leu Leu Leu Val Phe Ile Met Ser Val Phe Val Ala Ala Gly Leu Phe	
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Val Leu Val Met Lys Arg Arg Lys Lys Asn Gln Ser Asp His Thr Ser	
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685 690 695	
ggc ggc ggc ggc ggc acg ggc ggc cac cca cac gcg cac gtg cat cac	2224
Gly Gly Gly Gly Gly Thr Gly Gly His Pro His Ala His Val His His	
700 705 710	
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Arg Gly Pro Ala Leu Pro Lys Val Lys Thr Pro Ala Gly His Val Tyr	
715 720 725	
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Glu Tyr Ile Pro His Pro Leu Gly His Met Cys Lys Asn Pro Ile Tyr	
730 735 740	
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Arg Ser Arg Glu Gly Asn Ser Val Glu Asp Tyr Lys Asp Leu His Glu	
745 750 755 760	
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Leu Lys Val Thr Tyr Ser Ser Asn His His Leu Gln Gln Gln Gln Gln	
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Pro Pro Pro Pro Pro Gln Gln Pro Gln Gln Gln Pro Pro Gln Leu	
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cag ctg cag cct ggg gag gag gag agg cgg gaa agc cac cac ttg cgg	2512
Gln Leu Gln Pro Gly Glu Glu Glu Arg Arg Glu Ser His His Leu Arg	
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Ser Pro Ala Tyr Ser Val Ser Thr Ile Glu Pro Arg Glu Asp Leu Leu	
810 815 820	

34

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ccc aaa ttc ccg tgc agc ccc gct gct tac act ttc tcc ccc aac tat Pro Lys Phe Pro Cys Ser Pro Ala Ala Tyr Thr Phe Ser Pro Asn Tyr 860 865 870	2704
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 20 25 30

Cys Glu Glu Lys Asp Gly Ile Leu Thr Val Ser Cys Glu Asn Arg Gly
 35 40 45

Ile Ile Ser Leu Ser Glu Ile Ser Pro Pro Arg Phe Pro Ile Tyr His
 50 55 60

Leu Leu Leu Ser Gly Asn Leu Leu Asn Arg Leu Tyr Pro Asn Glu Phe
 65 70 75 80

Val Asn Tyr Thr Gly Ala Ser Ile Leu His Leu Gly Ser Asn Val Ile
 85 90 95

Gln Asp Ile Glu Thr Gly Ala Phe His Gly Leu Arg Gly Leu Arg Arg
 100 105 110

Leu His Leu Asn Asn Asn Lys Leu Glu Leu Leu Arg Asp Asp Thr Phe
 115 120 125

Leu Gly Leu Glu Asn Leu Glu Tyr Leu Gln Val Asp Tyr Asn Tyr Ile
 130 135 140

Ser Val Ile Glu Pro Asn Ala Phe Gly Lys Leu His Leu Leu Gln Val
 145 150 155 160

Leu Ile Leu Asn Asp Asn Leu Leu Ser Ser Leu Pro Asn Asn Leu Phe
 165 170 175

Arg Phe Val Pro Leu Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys
 180 185 190

Leu Leu Pro Tyr Val Gly Leu Leu Gln His Met Asp Lys Val Val Glu
 195 200 205

Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Ser Cys Glu Leu Ile Ser
 210 215 220

Leu Lys Asp Trp Leu Asp Ser Ile Ser Tyr Ser Ala Leu Val Gly Asp

37

Leu Phe Leu Gln Tyr Asn Leu Ile Arg Glu Ile Gln Ser Gly Thr Phe
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Asp Pro Val Pro Asn Leu Gln Leu Leu Phe Leu Asn Asn Asn Leu Leu
 485 490 495

Gln Ala Met Pro Ser Gly Val Phe Ser Gly Leu Thr Leu Leu Arg Leu
 500 505 510

Asn Leu Arg Ser Asn His Phe Thr Ser Leu Pro Val Ser Gly Val Leu
 515 520 525

Asp Gln Leu Lys Ser Leu Ile Gln Ile Asp Leu His Asp Asn Pro Trp
 530 535 540

Asp Cys Thr Cys Asp Ile Val Gly Met Lys Leu Trp Val Glu Gln Leu
 545 550 555 560

Lys Val Gly Val Leu Val Asp Glu Val Ile Cys Lys Ala Pro Lys Lys
 565 570 575

Phe Ala Glu Thr Asp Met Arg Ser Ile Lys Ser Glu Leu Leu Cys Pro
 580 585 590

Asp Tyr Ser Asp Val Val Val Ser Thr Pro Thr Pro Ser Ser Ile Gln
 595 600 605

Val Pro Ala Arg Thr Ser Ala Val Thr Pro Ala Val Arg Leu Asn Ser
 610 615 620

Thr Gly Ala Pro Ala Ser Leu Gly Ala Gly Gly Gly Ala Ser Ser Val
 625 630 635 640

Pro Leu Ser Val Leu Ile Leu Ser Leu Leu Leu Val Phe Ile Met Ser
 645 650 655

Val Phe Val Ala Ala Gly Leu Phe Val Leu Val Met Lys Arg Arg Lys
 660 665 670

Lys Asn Gln Ser Asp His Thr Ser Thr Asn Asn Ser Asp Val Ser Ser
 675 680 685

Phe Asn Met Gln Tyr Ser Val Tyr Gly Gly Gly Gly Gly Thr Gly Gly
 690 695 700

38

His Pro His Ala His Val His His Arg Gly Pro Ala Leu Pro Lys Val
705 710 715 720

Lys Thr Pro Ala Gly His Val Tyr Glu Tyr Ile Pro His Pro Leu Gly
725 730 735

His Met Cys Lys Asn Pro Ile Tyr Arg Ser Arg Glu Gly Asn Ser Val
740 745 750

Glu Asp Tyr Lys Asp Leu His Glu Leu Lys Val Thr Tyr Ser Ser Asn
755 760 765

His His Leu Gln Gln Gln Gln Gln Pro Pro Pro Pro Pro Gln Gln Pro
770 775 780

Gln Gln Gln Pro Pro Pro Gln Leu Gln Leu Gln Pro Gly Glu Glu Glu
785 790 795 800

Arg Arg Glu Ser His His Leu Arg Ser Pro Ala Tyr Ser Val Ser Thr
805 810 815

Ile Glu Pro Arg Glu Asp Leu Leu Ser Pro Val Gln Asp Ala Asp Arg
820 825 830

Phe Tyr Arg Gly Ile Leu Glu Pro Asp Lys His Cys Ser Thr Thr Pro
835 840 845

Ala Gly Asn Ser Leu Pro Glu Tyr Pro Lys Phe Pro Cys Ser Pro Ala
850 855 860

Ala Tyr Thr Phe Ser Pro Asn Tyr Asp Leu Arg Arg Pro His Gln Tyr
865 870 875 880

Leu His Pro Gly Ala Gly Asp Ser Arg Leu Arg Glu Pro Val Leu Tyr
885 890 895

Ser Pro Pro Ser Ala Val Phe Val Glu Pro Asn Arg Asn Glu Tyr Leu
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<213> Mus musculus

<400> 21

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 35 40 45
 Pro Gln Met Gln Met Gln Pro Gly Glu Glu Glu Arg Arg Glu Ser His
 50 55 60
 His Leu Arg Ser Pro Ala Tyr Ser Val Ser Thr Ile Glu Pro Arg Glu
 65 70 75 80

Asp Leu Leu Ser Pro Val Gln Asp Ala Asp Arg Phe Tyr Arg Gly Ile
85 90 95

Leu Glu Pro Asp Lys His Cys Ser Thr Thr Pro Ala Gly Ser Ser Leu
100 105 110

Pro Glu Tyr Pro Lys Phe Pro Cys Ser Pro Ala Ala Tyr Thr Phe Ser
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Pro	Asn	Tyr	Asp	Arg	Ser	Ala
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Met Lys
1

cct tcc ata gct gag atg ctt cac aga gga agg atg ttg tgg ata att 165
Pro Ser Ile Ala Glu Met Leu His Arg Gly Arg Met Leu Trp Ile Ile
5 10 15

ctt cta agc aca att gct cta gga tgg act acc ccg att ccc cta ata 213
Leu Leu Ser Thr Ile Ala Leu Gly Trp Thr Thr Pro Ile Pro Leu Ile
20 25 30

gag gac tca gag gaa ata gat gag ccc tgt ttt gat cca tgc tac tgt 261
Glu Asp Ser Glu Glu Ile Asp Glu Pro Cys Phe Asp Pro Cys Tyr Cys
35 40 45 50

gaa gtt aaa gaa agc ctc ttt cat ata cat tgt gac agt aaa gga ttt 309
Glu Val Lys Glu Ser Leu Phe His Ile His Cys Asp Ser Lys Gly Phe
55 60 65

41

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 Thr Asn Ile Ser Gln Ile Thr Glu Phe Trp Ser Arg Pro Phe Lys Leu
 70 75 80

tat ctg cag agg aat tct atg agg aaa tta tat acc aac agt ttt ctt 405
 Tyr Leu Gln Arg Asn Ser Met Arg Lys Leu Tyr Thr Asn Ser Phe Leu
 85 90 95

cat ttg aat aat gct gtg tct att aat ctt ggg aac aat gca ttg cag 453
 His Leu Asn Asn Ala Val Ser Ile Asn Leu Gly Asn Asn Ala Leu Gln
 100 105 110

gac att cag act gga gct ttc aat ggt ctt aag att tta aag aga cta 501
 Asp Ile Gln Thr Gly Ala Phe Asn Gly Leu Lys Ile Leu Lys Arg Leu
 115 120 125 130

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 Tyr Leu His Glu Asn Lys Leu Asp Val Phe Arg Asn Asp Thr Phe Leu
 135 140 145

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 Gly Leu Glu Ser Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Val Ile Lys
 150 155 160

cgt att gag agt ggg gca ttt cgg aac cta agt aaa ttg agg gtt ctg 645
 Arg Ile Glu Ser Gly Ala Phe Arg Asn Leu Ser Lys Leu Arg Val Leu
 165 170 175

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 Ile Leu Asn Asp Asn Leu Ile Pro Met Leu Pro Thr Asn Leu Phe Lys
 180 185 190

gct gtc tct tta acc cat ttg gac cta cgt gga aat agg tta aag gtt 741
 Ala Val Ser Leu Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys Val
 195 200 205 210

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 Leu Phe Tyr Arg Gly Met Leu Asp His Ile Gly Arg Ser Leu Met Glu
 215 220 225

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 Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Thr Cys Glu Ile Val Gln
 230 235 240

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 245 250 255

att acc tgt gag acc cct ttc cac ttc cat gga aag gac cta cga gaa 933
 Ile Thr Cys Glu Thr Pro Phe His Phe His Gly Lys Asp Leu Arg Glu
 260 265 270

atc agg aag aca gaa ctc tgt ccc ttg ttg tct gac tct gag gta gag 981
 Ile Arg Lys Thr Glu Leu Cys Pro Leu Leu Ser Asp Ser Glu Val Glu
 275 280 285 290

gct agt ttg gga att cca cat tcg tca tca agt aag gag aat gca tgg 1029
 Ala Ser Leu Gly Ile Pro His Ser Ser Ser Ser Lys Glu Asn Ala Trp

42

295	300	305	
cca act aag cct tcc tca atg cta tcc tct gtt cat ttt act gct tct Pro Thr Lys Pro Ser Ser Met Leu Ser Ser Val His Phe Thr Ala Ser			1077
310	315	320	
tct gtc gaa tac aag tcc tca aat aaa cag cct aag ccc acc aaa cag Ser Val Glu Tyr Lys Ser Ser Asn Lys Gln Pro Lys Pro Thr Lys Gln			1125
325	330	335	
cct cga aca cca agg cca ccc tcc acc tcc caa gct tta tat cct ggt Pro Arg Thr Pro Arg Pro Ser Thr Ser Gln Ala Leu Tyr Pro Gly			1173
340	345	350	
cca aac cag cct ccc att gct cct tat cag acc aga cca cca atc ccc Pro Asn Gln Pro Pro Ile Ala Pro Tyr Gln Thr Arg Pro Pro Ile Pro			1221
355	360	365	370
att ata tgc ccc act ggg tgt acc tgt aat ttg cac atc aat gac ctt Ile Ile Cys Pro Thr Gly Cys Thr Cys Asn Leu His Ile Asn Asp Leu			1269
375	380	385	
ggc ttg act gtc aac tgc aaa gag cga gga ttt aat aac att tct gaa Gly Leu Thr Val Asn Cys Lys Glu Arg Gly Phe Asn Asn Ile Ser Glu			1317
390	395	400	
ctt ctt cca agg ccc ttg aat gcc aag aaa ctg tat ctg agt agc aat Leu Leu Pro Arg Pro Leu Asn Ala Lys Lys Leu Tyr Leu Ser Ser Asn			1365
405	410	415	
ctg att cag aaa ata tac cgt tct gat ttt tgg aat ttt tct tcc ttg Leu Ile Gln Lys Ile Tyr Arg Ser Asp Phe Trp Asn Phe Ser Ser Leu			1413
420	425	430	
gat ctc ttg cat ctg ggg aac aat cgt att tcc tat gtc caa gat ggg Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ser Tyr Val Gln Asp Gly			1461
435	440	445	450
gcc ttt atc aac ttg ccc aac tta aag agc ctc ttc ctt aat ggc aac Ala Phe Ile Asn Leu Pro Asn Leu Lys Ser Leu Phe Leu Asn Gly Asn			1509
455	460	465	
gat ata gag aag ctg aca cca ggc atg ttc cga ggc cta cag agt ttg Asp Ile Glu Lys Leu Thr Pro Gly Met Phe Arg Gly Leu Gln Ser Leu			1557
470	475	480	
cac tac ttg tac ttt gag ttc aat gtc atc cgg gaa atc cag cct gca His Tyr Leu Tyr Phe Glu Phe Asn Val Ile Arg Glu Ile Gln Pro Ala			1605
485	490	495	
gcc ttc agc ctc atg ccc aac ttg aag ctg cta ttc ctc aat aat aac Ala Phe Ser Leu Met Pro Asn Leu Lys Leu Leu Phe Leu Asn Asn Asn			1653
500	505	510	
tta ctg agg act ctg cca aca gac gcc ttt gct ggc aca tcc ctg gcc Leu Leu Arg Thr Leu Pro Thr Asp Ala Phe Ala Gly Thr Ser Leu Ala			1701
515	520	525	530
cgg ctc aac ctg agg aag aac tac ttc ctc tat ctt ccc gtg gct ggt			1749

43

Arg	Leu	Asn	Leu	Arg	Lys	Asn	Tyr	Phe	Leu	Tyr	Leu	Pro	Val	Ala	Gly		
				535					540						545		
gtc	ctg	gaa	cac	ttg	aat	gcc	att	gtc	cag	ata	gac	ctc	aat	gag	aat		1797
Val	Leu	Glu	His	Leu	Asn	Ala	Ile	Val	Gln	Ile	Asp	Leu	Asn	Glu	Asn		
			550					555						560			
cct	tgg	gac	tgc	acc	tgt	gac	ctg	gtc	ccc	ttt	aaa	cag	tgg	atc	gaa		1845
Pro	Trp	Asp	Cys	Thr	Cys	Asp	Leu	Val	Pro	Phe	Lys	Gln	Trp	Ile	Glu		
			565				570							575			
acc	atc	agc	tca	gtc	agt	gtg	gtt	ggg	gat	gtg	ctt	tgc	agg	agc	cct		1893
Thr	Ile	Ser	Ser	Val	Ser	Val	Val	Gly	Asp	Val	Leu	Cys	Arg	Ser	Pro		
			580				585							590			
gag	aac	ctc	acg	cac	cgt	gat	gtg	cgc	act	att	gag	ctg	gaa	gtt	ctt		1941
Glu	Asn	Leu	Thr	His	Arg	Asp	Val	Arg	Thr	Ile	Glu	Leu	Glu	Val	Leu		
					600					605					610		
tgc	cca	gag	atg	ctg	cac	gtt	gca	cca	gct	gga	gaa	tcc	cca	gcc	cag		1989
Cys	Pro	Glu	Met	Leu	His	Val	Ala	Pro	Ala	Gly	Glu	Ser	Pro	Ala	Gln		
				615					620					625			
cct	gga	gat	tct	cac	ctt	att	ggg	gca	cca	acc	agt	gca	tca	cct	tat		2037
Pro	Gly	Asp	Ser	His	Leu	Ile	Gly	Ala	Pro	Thr	Ser	Ala	Ser	Pro	Tyr		
				630				635						640			
gag	ttt	tct	cct	cct	ggg	ggc	cct	gtg	cca	ctt	tct	gtg	tta	att	ctc		2085
Glu	Phe	Ser	Pro	Pro	Gly	Gly	Pro	Val	Pro	Leu	Ser	Val	Leu	Ile	Leu		
				645			650							655			
agc	ctg	ctg	gtt	ctg	ttt	ttc	tca	gca	gtc	ttt	gtt	gct	gca	ggc	ctc		2133
Ser	Leu	Leu	Val	Leu	Phe	Phe	Ser	Ala	Val	Phe	Val	Ala	Ala	Gly	Leu		
				660			665					670					
ttt	gcc	tac	gtg	ctc	cga	agg	cgt	cga	aag	aag	ctg	ccc	ttc	aga	agc		2181
Phe	Ala	Tyr	Val	Leu	Arg	Arg	Arg	Arg	Lys	Lys	Leu	Pro	Phe	Arg	Ser		
				675			680				685				690		
aag	cgg	cag	gaa	ggg	gtg	gac	ctt	act	ggc	atc	caa	atg	caa	tgc	cac		2229
Lys	Arg	Gln	Glu	Gly	Val	Asp	Leu	Thr	Gly	Ile	Gln	Met	Gln	Cys	His		
				695					700					705			
agg	ctg	ttt	gag	gat	ggg	gga	ggg	ggg	ggg	ggc	gga	agt	ggg	ggg	ggg		2277
Arg	Leu	Phe	Glu	Asp	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly		
				710				715						720			
ggg	cga	cca	act	ctt	tcc	tct	cca	gag	aag	gcc	cct	ccc	gtg	ggg	cat		2325
Gly	Arg	Pro	Thr	Leu	Ser	Ser	Pro	Glu	Lys	Ala	Pro	Pro	Val	Gly	His		
				725			730							735			
gtg	tat	gag	tac	atc	ccc	cac	ccg	gtt	acc	caa	atg	tgc	aac	aac	ccc		2373
Val	Tyr	Glu	Tyr	Ile	Pro	His	Pro	Val	Thr	Gln	Met	Cys	Asn	Asn	Pro		
				740			745							750			
atc	tac	aag	cct	cgt	gag	gag	gag	gag	gtg	gct	gtt	tca	tca	gcc	caa		2421
Ile	Tyr	Lys	Pro	Arg	Glu	Glu	Glu	Glu	Val	Ala	Val	Ser	Ser	Ala	Gln		
				755			760			765					770		

gaa gca ggg agt gca gaa cgt ggg ggt cca ggg aca caa cca ccg gga Glu Ala Gly Ser Ala Glu Arg Gly Gly Pro Gly Thr Gln Pro Pro Gly	2469
775 780 785	
atg ggt gag gct ctc cta gga agt gag cag ttt gct gag aca ccc aag Met Gly Glu Ala Leu Leu Gly Ser Glu Gln Phe Ala Glu Thr Pro Lys	2517
790 795 800	
gag aac cat agt aac tac cgg acc ttg ctg gaa aaa gag aag gag tgg Glu Asn His Ser Asn Tyr Arg Thr Leu Leu Glu Lys Glu Lys Glu Trp	2565
805 810 815	
gcc cta gca gtg tcc agc tcc cag ctt aac acc ata gtg acg gtg aat Ala Leu Ala Val Ser Ser Ser Gln Leu Asn Thr Ile Val Thr Val Asn	2613
820 825 830	
cac cat cac cct cac cac cca gca gtt ggt ggg gtt tca gga gta gtt His His His Pro His His Pro Ala Val Gly Gly Val Ser Gly Val Val	2661
835 840 845 850	
ggg gga act ggg gga gac ttg gca ggg ttc cgc cac cat gag aaa aat Gly Gly Thr Gly Gly Asp Leu Ala Gly Phe Arg His His Glu Lys Asn	2709
855 860 865	
ggt ggg gtg gtg ctg ttt cct cct ggg gga ggc tgt ggt agt ggc agt Gly Gly Val Val Leu Phe Pro Pro Gly Gly Gly Cys Gly Ser Gly Ser	2757
870 875 880	
atg cta cta gat cga gag agg cca cag cct gcc ccc tgc aca gtg gga Met Leu Leu Asp Arg Glu Arg Pro Gln Pro Ala Pro Cys Thr Val Gly	2805
885 890 895	
ttt gtg gac tgt ctc tat gga aca gtg ccc aaa tta aag gaa ctg cac Phe Val Asp Cys Leu Tyr Gly Thr Val Pro Lys Leu Lys Glu Leu His	2853
900 905 910	
gtg cac cct cct ggc atg caa tac cca gac tta cag cag gat gcc agg Val His Pro Pro Gly Met Gln Tyr Pro Asp Leu Gln Gln Asp Ala Arg	2901
915 920 925 930	
ctc aaa gaa acc ctt ctc ttc tgc gct gaa aag ggc ttc aca gac cac Leu Lys Glu Thr Leu Leu Phe Ser Ala Glu Lys Gly Phe Thr Asp His	2949
935 940 945	
caa acc caa aaa agt gat tac ctc gag tta agg gcc aaa ctt caa acc Gln Thr Gln Lys Ser Asp Tyr Leu Glu Leu Arg Ala Lys Leu Gln Thr	2997
950 955 960	
aag ccg gat tac ctc gaa gtc ctg gag aag aca aca tac agg ttc Lys Pro Asp Tyr Leu Glu Val Leu Glu Lys Thr Thr Tyr Arg Phe	3042
965 970 975	
taacagagag aagaaaatat attagtgcctt tttttttttc aaaagaaaag gaaaataaaa	3102
gaaatatatc ccttgctccc tttacacttg tcccagtaac tccatcctca cgatctttcc	3162
taccctgaac aaaactaaaa ccgcatgata actagagaat acagatgtat gctctccct	3222
ctcagatgcg atttgaggga agggccatac tcagatcatt aatcaatgaa agtgccttcg	3282

45

cagacttttg ccagcaaagtg ttatcattat ttttttatac tgaaacttga gactttgact 3342
 gtgccatgta taagatatac tggggatcat tgtatggatc ctaattaagt aaaattcaat 3402
 gtgtctttttt attttcagta actattttttt ttatagttgt agtttttgatt taaagggggg 3462
 gaaacaagtt gacattttgtc atttgtggct ttctttctta tcatcatggc acagattctg 3522
 tacatgtatt aacaatgcag ttt 3545

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<211> 977

<212> PRT

<213> Homo sapiens

<400> 23

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 20 25 30

Leu Ile Glu Asp Ser Glu Glu Ile Asp Glu Pro Cys Phe Asp Pro Cys
 35 40 45

Tyr Cys Glu Val Lys Glu Ser Leu Phe His Ile His Cys Asp Ser Lys
 50 55 60

Gly Phe Thr Asn Ile Ser Gln Ile Thr Glu Phe Trp Ser Arg Pro Phe
 65 70 75 80

Lys Leu Tyr Leu Gln Arg Asn Ser Met Arg Lys Leu Tyr Thr Asn Ser
 85 90 95

Phe Leu His Leu Asn Asn Ala Val Ser Ile Asn Leu Gly Asn Asn Ala
 100 105 110

Leu Gln Asp Ile Gln Thr Gly Ala Phe Asn Gly Leu Lys Ile Leu Lys
 115 120 125

Arg Leu Tyr Leu His Glu Asn Lys Leu Asp Val Phe Arg Asn Asp Thr
 130 135 140

Phe Leu Gly Leu Glu Ser Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Val
145 150 155 160

Ile Lys Arg Ile Glu Ser Gly Ala Phe Arg Asn Leu Ser Lys Leu Arg
165 170 175

Val Leu Ile Leu Asn Asp Asn Leu Ile Pro Met Leu Pro Thr Asn Leu
180 185 190

Phe Lys Ala Val Ser Leu Thr His Leu Asp Leu Arg Gly Asn Arg Leu
195 200 205

Lys Val Leu Phe Tyr Arg Gly Met Leu Asp His Ile Gly Arg Ser Leu
210 215 220

Met Glu Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Thr Cys Glu Ile
225 230 235 240

Val Gln Leu Lys Ser Trp Leu Glu Arg Ile Pro Tyr Thr Ala Leu Val
245 250 255

Gly Asp Ile Thr Cys Glu Thr Pro Phe His Phe His Gly Lys Asp Leu
260 265 270

Arg Glu Ile Arg Lys Thr Glu Leu Cys Pro Leu Leu Ser Asp Ser Glu
275 280 285

Val Glu Ala Ser Leu Gly Ile Pro His Ser Ser Ser Ser Lys Glu Asn
290 295 300

Ala Trp Pro Thr Lys Pro Ser Ser Met Leu Ser Ser Val His Phe Thr
305 310 315 320

Ala Ser Ser Val Glu Tyr Lys Ser Ser Asn Lys Gln Pro Lys Pro Thr
325 330 335

Lys Gln Pro Arg Thr Pro Arg Pro Pro Ser Thr Ser Gln Ala Leu Tyr
340 345 350

Pro Gly Pro Asn Gln Pro Pro Ile Ala Pro Tyr Gln Thr Arg Pro Pro
355 360 365

Ile Pro Ile Ile Cys Pro Thr Gly Cys Thr Cys Asn Leu His Ile Asn
370 375 380

Asp Leu Gly Leu Thr Val Asn Cys Lys Glu Arg Gly Phe Asn Asn Ile
 385 390 395 400

Ser Glu Leu Leu Pro Arg Pro Leu Asn Ala Lys Lys Leu Tyr Leu Ser
 405 410 415

Ser Asn Leu Ile Gln Lys Ile Tyr Arg Ser Asp Phe Trp Asn Phe Ser
 420 425 430

Ser Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ser Tyr Val Gln
 435 440 445

Asp Gly Ala Phe Ile Asn Leu Pro Asn Leu Lys Ser Leu Phe Leu Asn
 450 455 460

Gly Asn Asp Ile Glu Lys Leu Thr Pro Gly Met Phe Arg Gly Leu Gln
 465 470 475 480

Ser Leu His Tyr Leu Tyr Phe Glu Phe Asn Val Ile Arg Glu Ile Gln
 485 490 495

Pro Ala Ala Phe Ser Leu Met Pro Asn Leu Lys Leu Leu Phe Leu Asn
 500 505 510

Asn Asn Leu Leu Arg Thr Leu Pro Thr Asp Ala Phe Ala Gly Thr Ser
 515 520 525

Leu Ala Arg Leu Asn Leu Arg Lys Asn Tyr Phe Leu Tyr Leu Pro Val
 530 535 540

Ala Gly Val Leu Glu His Leu Asn Ala Ile Val Gln Ile Asp Leu Asn
 545 550 555 560

Glu Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Pro Phe Lys Gln Trp
 565 570 575

Ile Glu Thr Ile Ser Ser Val Ser Val Val Gly Asp Val Leu Cys Arg
 580 585 590

Ser Pro Glu Asn Leu Thr His Arg Asp Val Arg Thr Ile Glu Leu Glu
 595 600 605

Val Leu Cys Pro Glu Met Leu His Val Ala Pro Ala Gly Glu Ser Pro

48

610	615	620
Ala Gln Pro Gly Asp Ser His Leu Ile Gly Ala Pro Thr Ser Ala Ser 625 630 635 640		
Pro Tyr Glu Phe Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Val Leu 645 650 655		
Ile Leu Ser Leu Leu Val Leu Phe Phe Ser Ala Val Phe Val Ala Ala 660 665 670		
Gly Leu Phe Ala Tyr Val Leu Arg Arg Arg Arg Lys Lys Leu Pro Phe 675 680 685		
Arg Ser Lys Arg Gln Glu Gly Val Asp Leu Thr Gly Ile Gln Met Gln 690 695 700		
Cys His Arg Leu Phe Glu Asp Gly Gly Gly Gly Gly Gly Ser Gly 705 710 715 720		
Gly Gly Gly Arg Pro Thr Leu Ser Ser Pro Glu Lys Ala Pro Pro Val 725 730 735		
Gly His Val Tyr Glu Tyr Ile Pro His Pro Val Thr Gln Met Cys Asn 740 745 750		
Asn Pro Ile Tyr Lys Pro Arg Glu Glu Glu Glu Val Ala Val Ser Ser 755 760 765		
Ala Gln Glu Ala Gly Ser Ala Glu Arg Gly Gly Pro Gly Thr Gln Pro 770 775 780		
Pro Gly Met Gly Glu Ala Leu Leu Gly Ser Glu Gln Phe Ala Glu Thr 785 790 795 800		
Pro Lys Glu Asn His Ser Asn Tyr Arg Thr Leu Leu Glu Lys Glu Lys 805 810 815		
Glu Trp Ala Leu Ala Val Ser Ser Ser Gln Leu Asn Thr Ile Val Thr 820 825 830		
Val Asn His His His Pro His His Pro Ala Val Gly Gly Val Ser Gly 835 840 845		

49

Val Val Gly Gly Thr Gly Gly Asp Leu Ala Gly Phe Arg His His Glu
 850 855 860

Lys Asn Gly Gly Val Val Leu Phe Pro Pro Gly Gly Gly Cys Gly Ser
 865 870 875 880

Gly Ser Met Leu Leu Asp Arg Glu Arg Pro Gln Pro Ala Pro Cys Thr
 885 890 895

Val Gly Phe Val Asp Cys Leu Tyr Gly Thr Val Pro Lys Leu Lys Glu
 900 905 910

Leu His Val His Pro Pro Gly Met Gln Tyr Pro Asp Leu Gln Gln Asp
 915 920 925

Ala Arg Leu Lys Glu Thr Leu Leu Phe Ser Ala Glu Lys Gly Phe Thr
 930 935 940

Asp His Gln Thr Gln Lys Ser Asp Tyr Leu Glu Leu Arg Ala Lys Leu
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Gln Thr Lys Pro Asp Tyr Leu Glu Val Leu Glu Lys Thr Thr Tyr Arg
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Phe

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<211> 2631

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 atg ttt ctg tgg ctg ttt ctg att ttg tca gcc ctg att tct tcg aca 165
 Met Phe Leu Trp Leu Phe Leu Ile Leu Ser Ala Leu Ile Ser Ser Thr
 1 5 10 15
 aat gca gat tct gac ata tcg gtg gaa att tgc aat gtg tgt tcc tgc 213
 Asn Ala Asp Ser Asp Ile Ser Val Glu Ile Cys Asn Val Cys Ser Cys
 20 25 30
 gtg tca gtt gag aat gtg ctc tat gtc aac tgt gag aag gtt tca gtc 261
 Val Ser Val Glu Asn Val Leu Tyr Val Asn Cys Glu Lys Val Ser Val
 35 40 45
 tac aga cca aat cag ctg aaa cca cct tgg tct aat ttt tat cac ctc 309
 Tyr Arg Pro Asn Gln Leu Lys Pro Pro Trp Ser Asn Phe Tyr His Leu
 50 55 60
 aat ttc caa aat aat ttt tta aat att ctg tat cca aat aca ttc ttg 357
 Asn Phe Gln Asn Asn Phe Leu Asn Ile Leu Tyr Pro Asn Thr Phe Leu
 65 70 75 80
 aat ttt tca cat gca gtc tcc ctg cat ctg ggg aat aat aaa ctg cag 405
 Asn Phe Ser His Ala Val Ser Leu His Leu Gly Asn Asn Lys Leu Gln
 85 90 95
 aac att gag gga gga gcc ttt ctt ggg ctc agt gca tta aag cag ttg 453
 Asn Ile Glu Gly Gly Ala Phe Leu Gly Leu Ser Ala Leu Lys Gln Leu
 100 105 110
 cac ttg aac aac aat gaa tta aag att ctc cga gct gac act ttc ctt 501
 His Leu Asn Asn Asn Glu Leu Lys Ile Leu Arg Ala Asp Thr Phe Leu
 115 120 125
 ggc ata gag aac ttg gag tat ctc cag gct gac tac aat tta atc aag 549
 Gly Ile Glu Asn Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Leu Ile Lys
 130 135 140
 tat att gaa cga gga gcc ttc aat aag ctc cac aaa ctg aaa gtt ctc 597
 Tyr Ile Glu Arg Gly Ala Phe Asn Lys Leu His Lys Leu Lys Val Leu
 145 150 155 160
 att ctt aat gac aat ctg att tca ttc ctt cct gat aat att ttc cga 645
 Ile Leu Asn Asp Asn Leu Ile Ser Phe Leu Pro Asp Asn Ile Phe Arg
 165 170 175
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 Phe Ala Ser Leu Thr His Leu Asp Ile Arg Gly Asn Arg Ile Gln Lys
 180 185 190
 ctc cct tat atc ggg gtt ctg gaa cac att ggc cgt gtc gtt gaa ttg 741
 Leu Pro Tyr Ile Gly Val Leu Glu His Ile Gly Arg Val Val Glu Leu
 195 200 205
 caa ctg gaa gat aac cct tgg aac tgt agc tgt gat tta ttg ccc tta 789
 Gln Leu Glu Asp Asn Pro Trp Asn Cys Ser Cys Asp Leu Leu Pro Leu
 210 215 220
 aaa gct tgg ctg gag aac atg cca tat aac att tac ata gga gaa gct 837

52

tca gca ggc acc ttt gac tcc atg cca aat ttg cag tta ctg tac tta	1557
Ser Ala Gly Thr Phe Asp Ser Met Pro Asn Leu Gln Leu Leu Tyr Leu	
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aac aat aat ctc cta aag agc ctg cct gtt tac atc ttt tcc gga gca	1605
Asn Asn Asn Leu Leu Lys Ser Leu Pro Val Tyr Ile Phe Ser Gly Ala	
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ccc tta gct aga ctg aac ctg agg aac aac aaa ttc atg tac ctg cct	1653
Pro Leu Ala Arg Leu Asn Leu Arg Asn Asn Lys Phe Met Tyr Leu Pro	
500 505 510	
gtc agt ggg gtc ctt gat cag ttg caa tct ctt aca cag att gac ttg	1701
Val Ser Gly Val Leu Asp Gln Leu Gln Ser Leu Thr Gln Ile Asp Leu	
515 520 525	
gag ggc aac cca tgg gac tgt act tgt gac ttg gtg gca tta aag ctg	1749
Glu Gly Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Ala Leu Lys Leu	
530 535 540	
tgg gtg gag aag ttg agc gac ggg att gtt gtg aaa gaa ctg aaa tgt	1797
Trp Val Glu Lys Leu Ser Asp Gly Ile Val Val Lys Glu Leu Lys Cys	
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Glu Thr Pro Val Gln Phe Ala Asn Ile Glu Leu Lys Ser Leu Lys Asn	
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Glu Ile Leu Cys Pro Lys Leu Leu Asn Lys Pro Ser Ala Pro Phe Thr	
580 585 590	
agc cct gca cct gcc att aca ttc acc act cct ttg ggt ccc att cga	1941
Ser Pro Ala Pro Ala Ile Thr Phe Thr Thr Pro Leu Gly Pro Ile Arg	
595 600 605	
agt cct cct ggt ggg cca gtg cct ctg tct att tta atc tta agt atc	1989
Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Ile Leu Ile Leu Ser Ile	
610 615 620	
tta gtg gtc ctc att tta acg gtg ttt gtt gct ttt tgc ctt ctt gtt	2037
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Phe Val Leu Arg Arg Asn Lys Lys Pro Thr Val Lys His Glu Gly Leu	
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Gly Asn Pro Asp Cys Gly Ser Met Gln Leu Gln Leu Arg Lys His Asp	
660 665 670	
cac aaa acc aat aaa aaa gat gga ctg agc aca gaa gct ttc att cca	2181
His Lys Thr Asn Lys Lys Asp Gly Leu Ser Thr Glu Ala Phe Ile Pro	
675 680 685	
caa act ata gaa cag atg agc aag agc cac act tgt ggc ttg aaa gag	2229
Gln Thr Ile Glu Gln Met Ser Lys Ser His Thr Cys Gly Leu Lys Glu	
690 695 700	

53

tca gaa act ggg ttc atg ttt tca gat cct cca gga cag aaa gtt gtt 2277
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 705 710 715 720
 atg aga aat gtg gcc gac aag gag aaa gat tta tta cat gta gat acc 2325
 Met Arg Asn Val Ala Asp Lys Glu Lys Asp Leu Leu His Val Asp Thr
 725 730 735
 agg aag aga ctg agc aca att gat gag ctg gat gaa tta ttc cct agc 2373
 Arg Lys Arg Leu Ser Thr Ile Asp Glu Leu Asp Glu Leu Phe Pro Ser
 740 745 750
 agg gat tcc aat gtg ttt att cag aat ttt ctt gaa agc aaa aag gag 2421
 Arg Asp Ser Asn Val Phe Ile Gln Asn Phe Leu Glu Ser Lys Lys Glu
 755 760 765
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 Tyr Asn Ser Ile Gly Val Ser Gly Phe Glu Ile Arg Tyr Pro Glu Lys
 770 775 780
 caa cca gac aaa aaa agt aag aag tca ctg ata ggt ggc aac cac agt 2517
 Gln Pro Asp Lys Lys Ser Lys Lys Ser Leu Ile Gly Gly Asn His Ser
 785 790 795 800
 aaa att gtt gtg gaa caa agg aag agt gag tat ttt gaa ctg aag gcg 2565
 Lys Ile Val Val Glu Gln Arg Lys Ser Glu Tyr Phe Glu Leu Lys Ala
 805 810 815
 aaa ctg cag agt tcc cct gac tac cta cag gtc ctt gag gag caa aca 2613
 Lys Leu Gln Ser Ser Pro Asp Tyr Leu Gln Val Leu Glu Glu Gln Thr
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 gct ttg aac aag atc tag 2631
 Ala Leu Asn Lys Ile
 835

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<211> 837

<212> PRT

<213> Homo sapiens

<400> 25

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 20 25 30

Val Ser Val Glu Asn Val Leu Tyr Val Asn Cys Glu Lys Val Ser Val

54

35

40

45

Tyr Arg Pro Asn Gln Leu Lys Pro Pro Trp Ser Asn Phe Tyr His Leu
50 55 60

Asn Phe Gln Asn Asn Phe Leu Asn Ile Leu Tyr Pro Asn Thr Phe Leu
65 70 75 80

Asn Phe Ser His Ala Val Ser Leu His Leu Gly Asn Asn Lys Leu Gln
85 90 95

Asn Ile Glu Gly Gly Ala Phe Leu Gly Leu Ser Ala Leu Lys Gln Leu
100 105 110

His Leu Asn Asn Asn Glu Leu Lys Ile Leu Arg Ala Asp Thr Phe Leu
115 120 125

Gly Ile Glu Asn Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Leu Ile Lys
130 135 140

Tyr Ile Glu Arg Gly Ala Phe Asn Lys Leu His Lys Leu Lys Val Leu
145 150 155 160

Ile Leu Asn Asp Asn Leu Ile Ser Phe Leu Pro Asp Asn Ile Phe Arg
165 170 175

Phe Ala Ser Leu Thr His Leu Asp Ile Arg Gly Asn Arg Ile Gln Lys
180 185 190

Leu Pro Tyr Ile Gly Val Leu Glu His Ile Gly Arg Val Val Glu Leu
195 200 205

Gln Leu Glu Asp Asn Pro Trp Asn Cys Ser Cys Asp Leu Leu Pro Leu
210 215 220

Lys Ala Trp Leu Glu Asn Met Pro Tyr Asn Ile Tyr Ile Gly Glu Ala
225 230 235 240

Ile Cys Glu Thr Pro Ser Asp Leu Tyr Gly Arg Leu Leu Lys Glu Thr
245 250 255

Asn Lys Gln Glu Leu Cys Pro Met Gly Thr Gly Ser Asp Phe Asp Val
260 265 270

55

Arg Ile Leu Pro Pro Ser Gln Leu Glu Asn Gly Tyr Thr Thr Pro Asn
 275 280 285

Gly His Thr Thr Gln Thr Ser Leu His Arg Leu Val Thr Lys Pro Pro
 290 295 300

Lys Thr Thr Asn Pro Ser Lys Ile Ser Gly Ile Val Ala Gly Lys Ala
 305 310 315 320

Leu Ser Asn Arg Asn Leu Ser Gln Ile Val Ser Tyr Gln Thr Arg Val
 325 330 335

Pro Pro Leu Thr Pro Cys Pro Ala Pro Cys Phe Cys Lys Thr His Pro
 340 345 350

Ser Asp Leu Gly Leu Ser Val Asn Cys Gln Glu Lys Asn Ile Gln Ser
 355 360 365

Met Ser Glu Leu Ile Pro Lys Pro Leu Asn Ala Lys Lys Leu His Val
 370 375 380

Asn Gly Asn Ser Ile Lys Asp Val Asp Val Ser Asp Phe Thr Asp Phe
 385 390 395 400

Glu Gly Leu Asp Leu Leu His Leu Gly Ser Asn Gln Ile Thr Val Ile
 405 410 415

Lys Gly Asp Val Phe His Asn Leu Thr Asn Leu Arg Arg Leu Tyr Leu
 420 425 430

Asn Gly Asn Gln Ile Glu Arg Leu Tyr Pro Glu Ile Phe Ser Gly Leu
 435 440 445

His Asn Leu Gln Tyr Leu Tyr Leu Glu Tyr Asn Leu Ile Lys Glu Ile
 450 455 460

Ser Ala Gly Thr Phe Asp Ser Met Pro Asn Leu Gln Leu Leu Tyr Leu
 465 470 475 480

Asn Asn Asn Leu Leu Lys Ser Leu Pro Val Tyr Ile Phe Ser Gly Ala
 485 490 495

Pro Leu Ala Arg Leu Asn Leu Arg Asn Asn Lys Phe Met Tyr Leu Pro
 500 505 510

56

Val Ser Gly Val Leu Asp Gln Leu Gln Ser Leu Thr Gln Ile Asp Leu
 515 520 525

Glu Gly Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Ala Leu Lys Leu
 530 535 540

Trp Val Glu Lys Leu Ser Asp Gly Ile Val Val Lys Glu Leu Lys Cys
 545 550 555 560

Glu Thr Pro Val Gln Phe Ala Asn Ile Glu Leu Lys Ser Leu Lys Asn
 565 570 575

Glu Ile Leu Cys Pro Lys Leu Leu Asn Lys Pro Ser Ala Pro Phe Thr
 580 585 590

Ser Pro Ala Pro Ala Ile Thr Phe Thr Thr Pro Leu Gly Pro Ile Arg
 595 600 605

Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Ile Leu Ile Leu Ser Ile
 610 615 620

Leu Val Val Leu Ile Leu Thr Val Phe Val Ala Phe Cys Leu Leu Val
 625 630 635 640

Phe Val Leu Arg Arg Asn Lys Lys Pro Thr Val Lys His Glu Gly Leu
 645 650 655

Gly Asn Pro Asp Cys Gly Ser Met Gln Leu Gln Leu Arg Lys His Asp
 660 665 670

His Lys Thr Asn Lys Lys Asp Gly Leu Ser Thr Glu Ala Phe Ile Pro
 675 680 685

Gln Thr Ile Glu Gln Met Ser Lys Ser His Thr Cys Gly Leu Lys Glu
 690 695 700

Ser Glu Thr Gly Phe Met Phe Ser Asp Pro Pro Gly Gln Lys Val Val
 705 710 715 720

Met Arg Asn Val Ala Asp Lys Glu Lys Asp Leu Leu His Val Asp Thr
 725 730 735

Arg Lys Arg Leu Ser Thr Ile Asp Glu Leu Asp Glu Leu Phe Pro Ser
 740 745 750

57

Arg Asp Ser Asn Val Phe Ile Gln Asn Phe Leu Glu Ser Lys Lys Glu
 755 760 765

Tyr Asn Ser Ile Gly Val Ser Gly Phe Glu Ile Arg Tyr Pro Glu Lys
 770 775 780

Gln Pro Asp Lys Lys Ser Lys Lys Ser Leu Ile Gly Gly Asn His Ser
 785 790 795 800

Lys Ile Val Val Glu Gln Arg Lys Ser Glu Tyr Phe Glu Leu Lys Ala
 805 810 815

Lys Leu Gln Ser Ser Pro Asp Tyr Leu Gln Val Leu Glu Glu Gln Thr
 820 825 830

Ala Leu Asn Lys Ile
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<210> 26

<211> 1694

<212> DNA

<213> Homo sapiens

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 catctccaaa gaagtctttt ggaacaggaa aatcattcac cactcacagg gtcaaatatg 180
 aaatacaaaa ccacgaacca atcaacagaa tttttatcct tccaagatgc cagctcattg 240
 tacagaaaca ttttagaaaa agaaagggaa cttcagcaac tgggaatcac agaataccta 300
 aggaaaaaca ttgctcagct ccagcctgat atggaggcac attatcctgg agcccacgaa 360
 gagctgaagt taatggaaac attaatgtac tcacgtccaa ggaaggtatt agtggaaacag 420
 acaaaaaaatg agtattttga acttaaagct aatttacatg ctgaacctga ctatttagaa 480
 gtcctggagc agcaaacata gatggagagt ttgagggcctt tcgcagaaat gctgtgatcc 540
 tgttttaagt ccataccttg taaataagt ccttacgtga gtgtgtcatc aatcagaacc 600
 taagcacagc agtaaaactat ggggaaaaaa aaagaagaag aaaagaaact cagggatcac 660

58

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tgcattgtaaa tcattcaagg gttatagtaa tatttcatat actgaaaagt gtctcatagg      780
agtcctcttg cacatctaaa aaggctgaac atttaagtat cccgcaattt tcttgaattg      840
ctttccctat agattaatta caattggatt tcatcattta aaaaccatac ttgtatatgt      900
agttataata tgtaaggaat acattgttta taaccagtat gtacttcaaa aatgtgtatt      960
gtcaaacata cctaactttc ttgcaataaa tgcaaaagaa actggaactt gacaattata     1020
aatagtaata gtgaagaaaa aatagaaagg ttgcaattat ataggccatg ggtgggtcaa     1080
aactttgaac atttgagctt aaacaaatgc cactctcatg cattctaaat taaaaagtta     1140
aaatgattaa tagttcaggt ggaagaaata agcatacttt ttgggttttc tacacatttt     1200
gtgtagacaa ttttaatgtc agtgctgctg tgaactaaag tatgtcattt atgctcaaag     1260
tttaattctt cttcttgggg tattttaaaa atgctactga gattctgctg taaatatgac     1320
tagagaatat attgggtttg ctttatttca taggcttaat tctttgtaa tctgaatgac     1380
cataatagaa atacatttct tgtggcaagt aattcacagt tgtaaagtaa ataggaaaaa     1440
ttattttatt ttattgatg tacattgata gatgccataa atcagtagca aaaggcactt     1500
ctaaaggtaa gtggtttaag ttgcctcaag agagggacaa tgtagcttta ttttacaaga     1560
aggcatagtt agatttctat gaaatattta ttctgtacag ttttatatag ttttggttca     1620
caaaagtaat tattcttggg tgcctttcaa gaaaattaaa aatactactc actacaataa     1680
aactaaaatg aaaa                                           1694

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<210> 27

<211> 841

<212> PRT.

<213> Homo sapiens

<400> 27

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Met Lys Leu Trp Ile His Leu Phe Tyr Ser Ser Leu Leu Ala Cys Ile
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Ser Leu His Ser Gln Thr Pro Val Leu Ser Ser Arg Gly Ser Cys Asp
20           25           30

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Ser Leu Cys Asn Cys Glu Glu Lys Asp Gly Thr Met Leu Ile Asn Cys
35           40           45

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59

Glu Ala Lys Gly Ile Lys Met Val Ser Glu Ile Ser Val Pro Pro Ser
 50 55 60

Arg Pro Phe Gln Leu Ser Leu Leu Asn Asn Gly Leu Thr Met Leu His
 65 70 75 80

Thr Asn Asp Phe Ser Gly Leu Thr Asn Ala Ile Ser Ile His Leu Gly
 85 90 95

Phe Asn Asn Ile Ala Asp Ile Glu Ile Gly Ala Phe Asn Gly Leu Gly
 100 105 110

Leu Leu Lys Gln Leu His Ile Asn His Asn Ser Leu Glu Ile Leu Lys
 115 120 125

Glu Asp Thr Phe His Gly Leu Glu Asn Leu Glu Phe Leu Gln Ala Asp
 130 135 140

Asn Asn Phe Ile Thr Val Ile Glu Pro Ser Ala Phe Ser Lys Leu Asn
 145 150 155 160

Arg Leu Lys Val Leu Ile Leu Asn Asp Asn Ala Ile Glu Ser Leu Pro
 165 170 175

Pro Asn Ile Phe Arg Phe Val Pro Leu Thr His Leu Asp Leu Arg Gly
 180 185 190

Asn Gln Leu Gln Thr Leu Pro Tyr Val Gly Phe Leu Glu His Ile Gly
 195 200 205

Arg Ile Leu Asp Leu Gln Leu Glu Asp Asn Lys Trp Ala Cys Asn Cys
 210 215 220

Asp Leu Leu Gln Leu Lys Thr Trp Leu Glu Asn Met Pro Pro Gln Ser
 225 230 235 240

Ile Ile Gly Asp Val Val Cys Asn Ser Pro Pro Phe Phe Lys Gly Ser
 245 250 255

Ile Leu Ser Arg Leu Lys Lys Glu Ser Ile Cys Pro Thr Pro Pro Val
 260 265 270

Tyr Glu Glu His Glu Asp Pro Ser Gly Ser Leu His Leu Ala Ala Thr

60

275

280

285

Ser Ser Ile Asn Asp Ser Arg Met Ser Thr Lys Thr Thr Ser Ile Leu
 290 295 300

Lys Leu Pro Thr Lys Ala Pro Gly Leu Ile Pro Tyr Ile Thr Lys Pro
 305 310 315 320

Ser Thr Gln Leu Pro Gly Pro Tyr Cys Pro Ile Pro Cys Asn Cys Lys
 325 330 335

Val Leu Ser Pro Ser Gly Leu Leu Ile His Cys Gln Glu Arg Asn Ile
 340 345 350

Glu Ser Leu Ser Asp Leu Arg Pro Pro Pro Gln Asn Pro Arg Lys Leu
 355 360 365

Ile Leu Ala Gly Asn Ile Ile His Ser Leu Met Lys Ser Asp Leu Val
 370 375 380

Glu Tyr Phe Thr Leu Glu Met Leu His Leu Gly Asn Asn Arg Ile Glu
 385 390 395 400

Val Leu Glu Glu Gly Ser Phe Met Asn Leu Thr Arg Leu Gln Lys Leu
 405 410 415

Tyr Leu Asn Gly Asn His Leu Thr Lys Leu Ser Lys Gly Met Phe Leu
 420 425 430

Gly Leu His Asn Leu Glu Tyr Leu Tyr Leu Glu Tyr Asn Ala Ile Lys
 435 440 445

Glu Ile Leu Pro Gly Thr Phe Asn Pro Met Pro Lys Leu Lys Val Leu
 450 455 460

Tyr Leu Asn Asn Asn Leu Leu Gln Val Leu Pro Pro His Ile Phe Ser
 465 470 475 480

Gly Val Pro Leu Thr Lys Val Asn Leu Lys Thr Asn Gln Phe Thr His
 485 490 495

Leu Pro Val Ser Asn Ile Leu Asp Asp Leu Asp Leu Leu Thr Gln Ile
 500 505 510

61

Asp Leu Glu Asp Asn Pro Trp Asp Cys Ser Cys Asp Leu Val Gly Leu
 515 520 525

Gln Gln Trp Ile Gln Lys Leu Ser Lys Asn Thr Val Thr Asp Asp Ile
 530 535 540

Leu Cys Thr Ser Pro Gly His Leu Asp Lys Lys Glu Leu Lys Ala Leu
 545 550 555 560

Asn Ser Glu Ile Leu Cys Pro Gly Leu Val Asn Asn Pro Ser Met Pro
 565 570 575

Thr Gln Thr Ser Tyr Leu Met Val Thr Thr Pro Ala Thr Thr Thr Asn
 580 585 590

Thr Ala Asp Thr Ile Leu Arg Ser Leu Thr Asp Ala Val Pro Leu Ser
 595 600 605

Val Leu Ile Leu Gly Leu Leu Ile Met Phe Ile Thr Ile Val Phe Cys
 610 615 620

Ala Ala Gly Ile Val Val Leu Val Leu His Arg Arg Arg Arg Tyr Lys
 625 630 635 640

Lys Lys Gln Val Asp Glu Gln Met Arg Asp Asn Ser Pro Val His Leu
 645 650 655

Gln Tyr Ser Met Tyr Gly His Lys Thr Thr His His Thr Thr Glu Arg
 660 665 670

Pro Ser Ala Ser Leu Tyr Glu Gln His Met Val Ser Pro Met Val His
 675 680 685

Val Tyr Arg Ser Pro Ser Phe Gly Pro Lys His Leu Glu Glu Glu Glu
 690 695 700

Glu Arg Asn Glu Lys Glu Gly Ser Asp Ala Lys His Leu Gln Arg Ser
 705 710 715 720

Leu Leu Glu Gln Glu Asn His Ser Pro Leu Thr Gly Ser Asn Met Lys
 725 730 735

Tyr Lys Thr Thr Asn Gln Ser Thr Glu Phe Leu Ser Phe Gln Asp Ala
 740 745 750

62

Ser Ser Leu Tyr Arg Asn Ile Leu Glu Lys Glu Arg Glu Leu Gln Gln
 755 760 765

Leu Gly Ile Thr Glu Tyr Leu Arg Lys Asn Ile Ala Gln Leu Gln Pro
 770 775 780

Asp Met Glu Ala His Tyr Pro Gly Ala His Glu Glu Leu Lys Leu Met
 785 790 795 800

Glu Thr Leu Met Tyr Ser Arg Pro Arg Lys Val Leu Val Glu Gln Thr
 805 810 815

Lys Asn Glu Tyr Phe Glu Leu Lys Ala Asn Leu His Ala Glu Pro Asp
 820 825 830

Tyr Leu Glu Val Leu Glu Gln Gln Thr
 835 840

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<212> DNA

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<222> (1) .. (636)

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 1 5 10 15
 atc tac tgt tta ctc acg tat tgg atg gag gtg gtg ccc acc ctc ttg 96
 Ile Tyr Cys Leu Leu Thr Tyr Trp Met Glu Val Val Pro Thr Leu Leu
 20 25 30
 gca gag aca aag att cca gcc act gat gtc gct gat gcc agc ctg aat 144
 Ala Glu Thr Lys Ile Pro Ala Thr Asp Val Ala Asp Ala Ser Leu Asn
 35 40 45
 gaa tgt tcc agt acc gaa agg aaa caa gac gta gtg ttg ctg ttc gtg 192

63

Glu	Cys	Ser	Ser	Thr	Glu	Arg	Lys	Gln	Asp	Val	Val	Leu	Leu	Phe	Val		
50						55					60						
acc	ttg	tcc	cac	aca	cag	cca	cct	ctg	ttt	cac	ctg	cct	tat	gtc	cag		240
Thr	Leu	Ser	His	Thr	Gln	Pro	Pro	Leu	Phe	His	Leu	Pro	Tyr	Val	Gln		
65					70					75					80		
aaa	ccc	tta	atc	tct	aat	gtg	gag	cag	ctg	atc	ctg	ggg	atc	ccg	ggc		288
Lys	Pro	Leu	Ile	Ser	Asn	Val	Glu	Gln	Leu	Ile	Leu	Gly	Ile	Pro	Gly		
				85					90					95			
cag	aat	cgc	cgg	gag	ata	ggc	cat	ggc	cag	gat	atc	ttt	cca	gca	gag		336
Gln	Asn	Arg	Arg	Glu	Ile	Gly	His	Gly	Gln	Asp	Ile	Phe	Pro	Ala	Glu		
			100					105					110				
aag	ctc	tgc	cat	ctg	cag	gat	cgc	aag	gtg	aac	ctt	cac	aga	gct	gcc		384
Lys	Leu	Cys	His	Leu	Gln	Asp	Arg	Lys	Val	Asn	Leu	His	Arg	Ala	Ala		
		115					120				125						
tgg	ggc	gag	tgt	att	gtt	gca	ccc	aag	act	ctc	agc	ttc	tct	tac	tgt		432
Trp	Gly	Glu	Cys	Ile	Val	Ala	Pro	Lys	Thr	Leu	Ser	Phe	Ser	Tyr	Cys		
	130					135					140						
cag	ggg	acc	tgc	ccg	gcc	ctc	aac	agt	gag	ctc	cgt	cat	tcc	agc	ttt		480
Gln	Gly	Thr	Cys	Pro	Ala	Leu	Asn	Ser	Glu	Leu	Arg	His	Ser	Ser	Phe		
145					150					155					160		
gag	tgc	tat	aag	agg	gca	gta	cct	acc	tgt	ccc	tgg	ctc	ttc	cag	acc		528
Glu	Cys	Tyr	Lys	Arg	Ala	Val	Pro	Thr	Cys	Pro	Trp	Leu	Phe	Gln	Thr		
				165				170						175			
tgc	cgt	ccc	acc	atg	gtc	aga	ctc	ttc	tcc	ctg	atg	gtc	cag	gat	gac		576
Cys	Arg	Pro	Thr	Met	Val	Arg	Leu	Phe	Ser	Leu	Met	Val	Gln	Asp	Asp		
			180				185						190				
gaa	cac	aag	atg	agt	gtg	cac	tat	gtg	aac	act	tcc	ttg	gtg	gag	aag		624
Glu	His	Lys	Met	Ser	Val	His	Tyr	Val	Asn	Thr	Ser	Leu	Val	Glu	Lys		
		195					200					205					
tgt	ggc	tgc	tct	tga													639
Cys	Gly	Cys	Ser														
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Met	Val	Leu	Pro	Ser	Tyr	Ser	Lys	Ser	Glu	Gly	Gly	Ser	Leu	Leu	Asp		
1				5					10					15			

64

Ile Tyr Cys Leu Leu Thr Tyr Trp Met Glu Val Val Pro Thr Leu Leu
20 25 30

Ala Glu Thr Lys Ile Pro Ala Thr Asp Val Ala Asp Ala Ser Leu Asn
35 40 45

Glu Cys Ser Ser Thr Glu Arg Lys Gln Asp Val Val Leu Leu Phe Val
50 55 60

Thr Leu Ser His Thr Gln Pro Pro Leu Phe His Leu Pro Tyr Val Gln
65 70 75 80

Lys Pro Leu Ile Ser Asn Val Glu Gln Leu Ile Leu Gly Ile Pro Gly
85 90 95

Gln Asn Arg Arg Glu Ile Gly His Gly Gln Asp Ile Phe Pro Ala Glu
100 105 110

Lys Leu Cys His Leu Gln Asp Arg Lys Val Asn Leu His Arg Ala Ala
115 120 125

Trp Gly Glu Cys Ile Val Ala Pro Lys Thr Leu Ser Phe Ser Tyr Cys
130 135 140

Gln Gly Thr Cys Pro Ala Leu Asn Ser Glu Leu Arg His Ser Ser Phe
145 150 155 160

Glu Cys Tyr Lys Arg Ala Val Pro Thr Cys Pro Trp Leu Phe Gln Thr
165 170 175

Cys Arg Pro Thr Met Val Arg Leu Phe Ser Leu Met Val Gln Asp Asp
180 185 190

Glu His Lys Met Ser Val His Tyr Val Asn Thr Ser Leu Val Glu Lys
195 200 205

Cys Gly Cys Ser
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<212> DNA

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<222> (204) .. (860)

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155	160	165	170
gat atg gct ctt ttc aac agg gac tca gcc tta aaa tca tat agt att			761
Asp Met Ala Leu Phe Asn Arg Asp Ser Ala Leu Lys Ser Tyr Ser Ile			
	175	180	185
gaa aac gtt acc agc att gcc aac aac ttt cct gac ttt tct tac ttt			809
Glu Asn Val Thr Ser Ile Ala Asn Asn Phe Pro Asp Phe Ser Tyr Phe			
	190	195	200
aga acc ttc cca atg cca agc aac aaa agc tat gtt gtc aca ttt att			857
Arg Thr Phe Pro Met Pro Ser Asn Lys Ser Tyr Val Val Thr Phe Ile			
	205	210	215
tac tagcataata actgtgtcca gctgcctgga actttggcaa atgatgaata			910
Tyr			
atttgcagaa ggaatctgga aataaggccg tgagataggt atccctaccc acaactgtgc			970
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tgctctgtgc ccaactgcca gaacactttt g			1061
<210>	31		
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<213>	Homo sapiens		
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Met Ala Pro Pro Ser Arg His Cys Leu Leu Leu Ile Ser Thr Leu Gly			
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Val Phe Ala Leu Asn Cys Phe Thr Lys Gly Gln Lys Asn Ser Thr Leu			
	20	25	30
Ile Phe Thr Arg Glu Asn Thr Ile Arg Asn Cys Ser Cys Ser Ala Asp			
	35	40	45
Ile Arg Asp Cys Asp Tyr Ser Leu Ala Asn Leu Met Cys Asn Cys Lys			
	50	55	60
Thr Val Leu Pro Leu Ala Val Glu Arg Thr Ser Tyr Asn Gly His Leu			
	65	70	75
			80

67

Thr Ile Trp Phe Thr Asp Thr Ser Ala Leu Gly His Leu Leu Asn Phe
 85 90 95

Thr Leu Val Gln Asp Leu Lys Leu Ser Leu Cys Ser Thr Asn Thr Leu
 100 105 110

Pro Thr Glu Tyr Leu Ala Ile Cys Gly Leu Lys Arg Leu Arg Ile Asn
 115 120 125

Met Glu Ala Lys His Pro Phe Pro Glu Gln Ser Leu Leu Ile His Ser
 130 135 140

Gly Gly Asp Ser Asp Ser Arg Glu Lys Pro Met Trp Leu His Lys Gly
 145 150 155 160

Trp Gln Pro Cys Met Tyr Ile Ser Phe Leu Asp Met Ala Leu Phe Asn
 165 170 175

Arg Asp Ser Ala Leu Lys Ser Tyr Ser Ile Glu Asn Val Thr Ser Ile
 180 185 190

Ala Asn Asn Phe Pro Asp Phe Ser Tyr Phe Arg Thr Phe Pro Met Pro
 195 200 205

Ser Asn Lys Ser Tyr Val Val Thr Phe Ile Tyr
 210 215

<210> 32

<211> 921

<212> DNA

<213> Mus musculus

<220>

<221> CDS

<222> (255) .. (890)

<223>

<400> 32

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ctagagcacg tttatgcgca ccacgggagc acatgctatc agtgctggcg gagagtgttg	180
gggtaaggag gtgacctaca atggactggc tcatgaggga gaaacaggaa cacaccagtc	240
catgctggac aaga atg aca tca cct tcc agc ttc tgc ctc ctt ctg ctc	290
Met Thr Ser Pro Ser Ser Phe Cys Leu Leu Leu Leu	
1 5 10	
caa gcg cta ggc atc gtt gcc ctt ggc cac ttc aca aaa gct cag aac	338
Gln Ala Leu Gly Ile Val Ala Leu Gly His Phe Thr Lys Ala Gln Asn	
15 20 25	
aac aca ctg att ttc aca aaa gga aat acc att cgc aac tgc agc tgc	386
Asn Thr Leu Ile Phe Thr Lys Gly Asn Thr Ile Arg Asn Cys Ser Cys	
30 35 40	
cca gta gac atc agg gac tgt gac tac agt ttg gct aac ttg ata tgc	434
Pro Val Asp Ile Arg Asp Cys Asp Tyr Ser Leu Ala Asn Leu Ile Cys	
45 50 55 60	
agc tgt aag tct atc ctg cct tct gcc atg gag caa acc agc tat cat	482
Ser Cys Lys Ser Ile Leu Pro Ser Ala Met Glu Gln Thr Ser Tyr His	
65 70 75	
ggc cat ctg acc atc tgg ttc aca gat ata tcc aca ttg ggc cac gtg	530
Gly His Leu Thr Ile Trp Phe Thr Asp Ile Ser Thr Leu Gly His Val	
80 85 90	
ctg aag ttc act ctg gtc caa gac ttg aag ctt tcc cta tgt ggt tcc	578
Leu Lys Phe Thr Leu Val Gln Asp Leu Lys Leu Ser Leu Cys Gly Ser	
95 100 105	
agc acc ttc ccc acc aag tac ctg gct atc tgt ggg ctg cag agg ctt	626
Ser Thr Phe Pro Thr Lys Tyr Leu Ala Ile Cys Gly Leu Gln Arg Leu	
110 115 120	
cgc atc cat act aag gcc agg cat ccc tcc cgg ggg cag agt ttg ctc	674
Arg Ile His Thr Lys Ala Arg His Pro Ser Arg Gly Gln Ser Leu Leu	
125 130 135 140	
atc cac agc aga agg gaa ggc agt tcc ttg tac aaa ggc tgg caa aca	722
Ile His Ser Arg Arg Glu Gly Ser Ser Leu Tyr Lys Gly Trp Gln Thr	
145 150 155	
tgt atg ttc atc tca ttc tta gat gtg gct ctt ttc aac ggg gac tca	770
Cys Met Phe Ile Ser Phe Leu Asp Val Ala Leu Phe Asn Gly Asp Ser	
160 165 170	
tct tta aag tca tac agt att gac aac att tct agc ctc gcc agt gac	818
Ser Leu Lys Ser Tyr Ser Ile Asp Asn Ile Ser Ser Leu Ala Ser Asp	
175 180 185	
ttt cct gac ttt tct tac ttt aaa acg tcc cca atg cca agc aac aga	866
Phe Pro Asp Phe Ser Tyr Phe Lys Thr Ser Pro Met Pro Ser Asn Arg	
190 195 200	

69

agc tat gtt gtc aca gtt att tac tagcatcctg tgtccctcca ccaggaactc 920
 Ser Tyr Val Val Thr Val Ile Tyr
 205 210

t 921

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<212> PRT

<213> Mus musculus

<400> 33

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Ile Val Ala Leu Gly His Phe Thr Lys Ala Gln Asn Asn Thr Leu Ile
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Phe Thr Lys Gly Asn Thr Ile Arg Asn Cys Ser Cys Pro Val Asp Ile
 35 40 45

Arg Asp Cys Asp Tyr Ser Leu Ala Asn Leu Ile Cys Ser Cys Lys Ser
 50 55 60

Ile Leu Pro Ser Ala Met Glu Gln Thr Ser Tyr His Gly His Leu Thr
 65 70 75 80

Ile Trp Phe Thr Asp Ile Ser Thr Leu Gly His Val Leu Lys Phe Thr
 85 90 95

Leu Val Gln Asp Leu Lys Leu Ser Leu Cys Gly Ser Ser Thr Phe Pro
 100 105 110

Thr Lys Tyr Leu Ala Ile Cys Gly Leu Gln Arg Leu Arg Ile His Thr
 115 120 125

Lys Ala Arg His Pro Ser Arg Gly Gln Ser Leu Leu Ile His Ser Arg
 130 135 140

Arg Glu Gly Ser Ser Leu Tyr Lys Gly Trp Gln Thr Cys Met Phe Ile
 145 150 155 160

70

Ser Phe Leu Asp Val Ala Leu Phe Asn Gly Asp Ser Ser Leu Lys Ser
 165 170 175

Tyr Ser Ile Asp Asn Ile Ser Ser Leu Ala Ser Asp Phe Pro Asp Phe
 180 185 190

Ser Tyr Phe Lys Thr Ser Pro Met Pro Ser Asn Arg Ser Tyr Val Val
 195 200 205

Thr Val Ile Tyr
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<210> 34

<211> 693

<212> DNA

<213> Homo sapiens

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<221> CDS

<222> (1)..(690)

<223>

<400> 34

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 Met Ala Ser Leu Gly Leu Gln Leu Val Gly Tyr Ile Leu Gly Leu Leu
 1 5 10 15

ggg ctt ttg ggc aca ctg gtt gcc atg ctg ctc ccc agc tgg aaa aca 96
 Gly Leu Leu Gly Thr Leu Val Ala Met Leu Leu Pro Ser Trp Lys Thr
 20 25 30

agt tct tat gtc ggt gcc agc att gtg aca gca gtt ggc ttc tcc aag 144
 Ser Ser Tyr Val Gly Ala Ser Ile Val Thr Ala Val Gly Phe Ser Lys
 35 40 45

ggc ctc tgg atg gaa tgt gcc aca cac agc aca ggc atc acc cag tgt 192
 Gly Leu Trp Met Glu Cys Ala Thr His Ser Thr Gly Ile Thr Gln Cys
 50 55 60

gac atc tat agc acc ctt ctg ggc ctg ccc gct gac atc cag ggt gcc 240
 Asp Ile Tyr Ser Thr Leu Leu Gly Leu Pro Ala Asp Ile Gln Gly Ala
 65 70 75 80

cag gcc atg atg gtg aca tcc agt gca atc tcc tcc ctg gcc tgc att 288

71

Gln Ala Met Met Val Thr Ser Ser Ala Ile Ser Ser Leu Ala Cys Ile
85 90 95

atc tct gtg gtg ggc atg aga tgc aca gtc ttc tgc cag gaa tcc cga 336
Ile Ser Val Val Gly Met Arg Cys Thr Val Phe Cys Gln Glu Ser Arg
100 105 110

gcc aaa gac aga gtg gcg gta gca ggt gga gtc ttt ttc atc ctt gga 384
Ala Lys Asp Arg Val Ala Val Ala Gly Gly Val Phe Phe Ile Leu Gly
115 120 125

ggc ctc ctg gga ttc att cct gtt gcc tgg aat ctt cat ggg atc cta 432
Gly Leu Leu Gly Phe Ile Pro Val Ala Trp Asn Leu His Gly Ile Leu
130 135 140

cgg gac ttc tac tca cca ctg gtg cct gac agc atg aaa ttt gag att 480
Arg Asp Phe Tyr Ser Pro Leu Val Pro Asp Ser Met Lys Phe Glu Ile
145 150 155 160

gga gag gct ctt tac ttg ggc att att tct tcc ctg ttc tcc ctg ata 528
Gly Glu Ala Leu Tyr Leu Gly Ile Ile Ser Ser Leu Phe Ser Leu Ile
165 170 175

gct gga atc atc ctc tgc ttt tcc tgc tca tcc cag aga aat cgc tcc 576
Ala Gly Ile Ile Leu Cys Phe Ser Cys Ser Ser Gln Arg Asn Arg Ser
180 185 190

aac tac tac gat gcc tac caa gcc caa cct ctt gcc aca agg agc tct 624
Asn Tyr Tyr Asp Ala Tyr Gln Ala Gln Pro Leu Ala Thr Arg Ser Ser
195 200 205

cca agg gct ggt caa cct ccc aaa gtc aag agt gag ttc aat tcc tac 672
Pro Arg Ala Gly Gln Pro Pro Lys Val Lys Ser Glu Phe Asn Ser Tyr
210 215 220

agc ctg aca ggg tat gtg tga 693
Ser Leu Thr Gly Tyr Val
225 230

<210> 35

<211> 230

<212> PRT

<213> Homo sapiens

<400> 35

Met Ala Ser Leu Gly Leu Gln Leu Val Gly Tyr Ile Leu Gly Leu Leu
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Gly Leu Leu Gly Thr Leu Val Ala Met Leu Leu Pro Ser Trp Lys Thr
20 25 30

72

Ser Ser Tyr Val Gly Ala Ser Ile Val Thr Ala Val Gly Phe Ser Lys
 35 40 45

Gly Leu Trp Met Glu Cys Ala Thr His Ser Thr Gly Ile Thr Gln Cys
 50 55 60

Asp Ile Tyr Ser Thr Leu Leu Gly Leu Pro Ala Asp Ile Gln Gly Ala
 65 70 75 80

Gln Ala Met Met Val Thr Ser Ser Ala Ile Ser Ser Leu Ala Cys Ile
 85 90 95

Ile Ser Val Val Gly Met Arg Cys Thr Val Phe Cys Gln Glu Ser Arg
 100 105 110

Ala Lys Asp Arg Val Ala Val Ala Gly Gly Val Phe Phe Ile Leu Gly
 115 120 125

Gly Leu Leu Gly Phe Ile Pro Val Ala Trp Asn Leu His Gly Ile Leu
 130 135 140

Arg Asp Phe Tyr Ser Pro Leu Val Pro Asp Ser Met Lys Phe Glu Ile
 145 150 155 160

Gly Glu Ala Leu Tyr Leu Gly Ile Ile Ser Ser Leu Phe Ser Leu Ile
 165 170 175

Ala Gly Ile Ile Leu Cys Phe Ser Cys Ser Ser Gln Arg Asn Arg Ser
 180 185 190

Asn Tyr Tyr Asp Ala Tyr Gln Ala Gln Pro Leu Ala Thr Arg Ser Ser
 195 200 205

Pro Arg Ala Gly Gln Pro Pro Lys Val Lys Ser Glu Phe Asn Ser Tyr
 210 215 220

Ser Leu Thr Gly Tyr Val
 225 230

<210> 36

<211> 1002

<212> DNA

<213> Homo sapiens

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<222> (998)..(998)

<223> unknown amino

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tggcaaccca tgccttagaa atcgctgggc tgtttcttgg tgggtgttga atggtgggca      180
cagtggctgt cactgtcatg cctcagtgga gagtgtcggc cttcattgaa aacaacatcg      240
tggtttttga aaacttctgg gaaggactgt ggatgaattg cgtgaggcag gctaacatca      300
ggatgcagtg caaaatctat gattccctgc tggctctttc tccggaccta caggcagcca      360
gaggactgat gtgtgctgct tccgtgatgt ccttcttggc tttcatgatg gccatccttg      420
gcatgaaatg caccaggtgc acggggggaca atgagaaggt gaaagctcac attctgctga      480
cggctggaat caatctcatc atcacgggca tgggtggggc caaccctgtg aacctggttt      540
ccaatgccat catcagagat ttttttacct caatagtga tgttgcccaa aaacgtgagc      600
ttggagaagc tctotactta ggatggacca cggcactggg gctsatgtgt ggaggagctc      660
tgttctgctg cgtttttttgy tgcaacgaaa agagcagtag ctacagatac tcgatacctt      720
cccatcgcac aacccaaaaa agttatcaca ccggaaagaa gtcaccgagc gtctactcca      780
gaagtcagta tgtgtagttg tgtatgtttt ttttaacttta ctataaagcc atgcaaata      840
caaaaatcta tattactttc tcaaaatgga ccccaaagaa actttgattt actgttctta      900
actgccta attaattaca ggaactgtgc atcagctatt tatgattcta taagctattt      960
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<210> 37

<211> 225

<212> PRT

<213> Homo sapiens

<400> 37

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 20 25 30

Ser Ala Phe Ile Glu Asn Asn Ile Val Val Phe Glu Asn Phe Trp Glu
 35 40 45

Gly Leu Trp Met Asn Cys Val Arg Gln Ala Asn Ile Arg Met Gln Cys
 50 55 60

Lys Ile Tyr Asp Ser Leu Leu Ala Leu Ser Pro Asp Leu Gln Ala Ala
 65 70 75 80

Arg Gly Leu Met Cys Ala Ala Ser Val Met Ser Phe Leu Ala Phe Met
 85 90 95

Met Ala Ile Leu Gly Met Lys Cys Thr Arg Cys Thr Gly Asp Asn Glu
 100 105 110

Lys Val Lys Ala His Ile Leu Leu Thr Ala Gly Ile Asn Leu Ile Ile
 115 120 125

Thr Gly Met Val Gly Ala Asn Pro Val Asn Leu Val Ser Asn Ala Ile
 130 135 140

Ile Arg Asp Phe Phe Thr Pro Ile Val Asn Val Ala Gln Lys Arg Glu
 145 150 155 160

Leu Gly Glu Ala Leu Tyr Leu Gly Trp Thr Thr Ala Leu Val Leu Ile
 165 170 175

Val Gly Gly Ala Leu Phe Cys Cys Val Phe Cys Cys Asn Glu Lys Ser
 180 185 190

Ser Ser Tyr Arg Tyr Ser Ile Pro Ser His Arg Thr Thr Gln Lys Ser
 195 200 205

Tyr His Thr Gly Lys Lys Ser Pro Ser Val Tyr Ser Arg Ser Gln Tyr
 210 215 220

75

Val
225

<210> 38

<211> 833

<212> DNA

<213> Homo sapiens

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<222> (159)..(830)

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catcatcaaaa gacttctcta gactcaaaag gcttccacgt totacatctt gagcatcttc      120
taccactccg aattgaacca gtcttcaaag taaaggca atg gca ttt tat ccc ttg      176
                                         Met Ala Phe Tyr Pro Leu
                                         1             5

caa att gct ggg ctg gtt ctt ggg ttc ctt ggc atg gtg ggg act ctt      224
Gln Ile Ala Gly Leu Val Leu Gly Phe Leu Gly Met Val Gly Thr Leu
                        10                        15                        20

gcc aca acc ctt ctg cct cag tgg aga gta tca gct ttt gtt ggc agc      272
Ala Thr Thr Leu Leu Pro Gln Trp Arg Val Ser Ala Phe Val Gly Ser
                        25                        30                        35

aac att att gtc ttt gag agg ctc tgg gaa ggg ctc tgg atg aat tgc      320
Asn Ile Ile Val Phe Glu Arg Leu Trp Glu Gly Leu Trp Met Asn Cys
                        40                        45                        50

atc cga caa gcc agg gtc cgg ttg caa tgc aag ttc tat agc tcc ttg      368
Ile Arg Gln Ala Arg Val Arg Leu Gln Cys Lys Phe Tyr Ser Ser Leu
55                        60                        65                        70

ttg gct ctc ccg cct gcc ctg gaa aca gcc cgg gcc ctc atg tgt gtg      416
Leu Ala Leu Pro Pro Ala Leu Glu Thr Ala Arg Ala Leu Met Cys Val
                        75                        80                        85

gct gtt gct ctc tcc ttg atc gcc ctg ctt att ggc atc tgt ggc atg      464
Ala Val Ala Leu Ser Leu Ile Ala Leu Leu Ile Gly Ile Cys Gly Met
                        90                        95                        100

aag cag gtc cag tgc aca ggc tct aac gag agg gcc aaa gca tac ctt      512

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76

Lys Gln Val Gln Cys Thr Gly Ser Asn Glu Arg Ala Lys Ala Tyr Leu
 105 110 115
 ctg gga act tca gga gtc ctc ttc atc ctg acg ggt atc ttc gtt ctg 560
 Leu Gly Thr Ser Gly Val Leu Phe Ile Leu Thr Gly Ile Phe Val Leu
 120 125 130
 att ccg gtg agc tgg aca gcc aat ata atc atc aga gat ttc tac aac 608
 Ile Pro Val Ser Trp Thr Ala Asn Ile Ile Ile Arg Asp Phe Tyr Asn
 135 140 145 150
 cca gcc atc cac ata ggt cag aaa cga gag ctg gga gca gca ctt ttc 656
 Pro Ala Ile His Ile Gly Gln Lys Arg Glu Leu Gly Ala Ala Leu Phe
 155 160 165
 ctt ggc tgg gca agc gct gct gtc ctc ttc att gga ggg ggt ctg ctt 704
 Leu Gly Trp Ala Ser Ala Ala Val Leu Phe Ile Gly Gly Gly Leu Leu
 170 175 180
 tgt gga ttt tgc tgc tgc aac aga aag aag caa ggg tac aga tat cca 752
 Cys Gly Phe Cys Cys Cys Asn Arg Lys Lys Gln Gly Tyr Arg Tyr Pro
 185 190 195
 gtg cct ggc tac cgt gtg cca cac aca gat aag cga aga aat acg aca 800
 Val Pro Gly Tyr Arg Val Pro His Thr Asp Lys Arg Arg Asn Thr Thr
 200 205 210
 atg ctt agt aag acc tcc acc agt tat gtc taa 833
 Met Leu Ser Lys Thr Ser Thr Ser Tyr Val
 215 220

<210> 39

<211> 224

<212> PRT

<213> Homo sapiens

<400> 39

Met Ala Phe Tyr Pro Leu Gln Ile Ala Gly Leu Val Leu Gly Phe Leu
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 Gly Met Val Gly Thr Leu Ala Thr Thr Leu Leu Pro Gln Trp Arg Val
 20 25 30
 Ser Ala Phe Val Gly Ser Asn Ile Ile Val Phe Glu Arg Leu Trp Glu
 35 40 45
 Gly Leu Trp Met Asn Cys Ile Arg Gln Ala Arg Val Arg Leu Gln Cys
 50 55 60

77

Lys Phe Tyr Ser Ser Leu Leu Ala Leu Pro Pro Ala Leu Glu Thr Ala
65 70 75 80

Arg Ala Leu Met Cys Val Ala Val Ala Leu Ser Leu Ile Ala Leu Leu
85 90 95

Ile Gly Ile Cys Gly Met Lys Gln Val Gln Cys Thr Gly Ser Asn Glu
100 105 110

Arg Ala Lys Ala Tyr Leu Leu Gly Thr Ser Gly Val Leu Phe Ile Leu
115 120 125

Thr Gly Ile Phe Val Leu Ile Pro Val Ser Trp Thr Ala Asn Ile Ile
130 135 140

Ile Arg Asp Phe Tyr Asn Pro Ala Ile His Ile Gly Gln Lys Arg Glu
145 150 155 160

Leu Gly Ala Ala Leu Phe Leu Gly Trp Ala Ser Ala Ala Val Leu Phe
165 170 175

Ile Gly Gly Gly Leu Leu Cys Gly Phe Cys Cys Cys Asn Arg Lys Lys
180 185 190

Gln Gly Tyr Arg Tyr Pro Val Pro Gly Tyr Arg Val Pro His Thr Asp
195 200 205

Lys Arg Arg Asn Thr Thr Met Leu Ser Lys Thr Ser Thr Ser Tyr Val
210 215 220

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<211> 393

<212> DNA

<213> Homo sapiens

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<222> (1) .. (390)

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 1 5 10 15

ggg att gcg ggc atc att gct gcc acc tgc atg gcc cag tgg agc acc 96
 Gly Ile Ala Gly Ile Ile Ala Ala Thr Cys Met Ala Gln Trp Ser Thr
 20 25 30

caa gac ttg tac aac aac ccc gta aca gct gtt ttc aac tac cag ggg 144
 Gln Asp Leu Tyr Asn Asn Pro Val Thr Ala Val Phe Asn Tyr Gln Gly
 35 40 45

ctg tgg cgc tcc tgt gtc cga gag agc tct ggc ttc acc gag tgc cgg 192
 Leu Trp Arg Ser Cys Val Arg Glu Ser Ser Gly Phe Thr Glu Cys Arg
 50 55 60

ggc tac ttc acc ctg ctg ggg ctg cca ggt aag ggc cag gtg tct ggc 240
 Gly Tyr Phe Thr Leu Leu Gly Leu Pro Gly Lys Gly Gln Val Ser Gly
 65 70 75 80

tgg ctg gag gga gag att gga ggt gga gag gaa act gca ggc tct gtc 288
 Trp Leu Glu Gly Glu Ile Gly Gly Glu Glu Thr Ala Gly Ser Val
 85 90 95

tgg gca cca cga cag gga ctg ctg ggg agg gag gaa ctg cga ttc gtg 336
 Trp Ala Pro Arg Gln Gly Leu Leu Gly Arg Glu Glu Leu Arg Phe Val
 100 105 110

ttt gac agg ggc aac agc cac ctg cac cag ggt gga ata gga gga cgg 384
 Phe Asp Arg Gly Asn Ser His Leu His Gln Gly Gly Ile Gly Gly Arg
 115 120 125

gaa cct tag 393
 Glu Pro
 130

<210> 41

<211> 130

<212> PRT

<213> Homo sapiens

<400> 41

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 1 5 10 15

Gly Ile Ala Gly Ile Ile Ala Ala Thr Cys Met Ala Gln Trp Ser Thr
 20 25 30

79

Gln Asp Leu Tyr Asn Asn Pro Val Thr Ala Val Phe Asn Tyr Gln Gly
35 40 45

Leu Trp Arg Ser Cys Val Arg Glu Ser Ser Gly Phe Thr Glu Cys Arg
50 55 60

Gly Tyr Phe Thr Leu Leu Gly Leu Pro Gly Lys Gly Gln Val Ser Gly
65 70 75 80

Trp Leu Glu Gly Glu Ile Gly Gly Gly Glu Glu Thr Ala Gly Ser Val
85 90 95

Trp Ala Pro Arg Gln Gly Leu Leu Gly Arg Glu Glu Leu Arg Phe Val
100 105 110

Phe Asp Arg Gly Asn Ser His Leu His Gln Gly Gly Ile Gly Gly Arg
115 120 125

Glu Pro
130

<210> 42

<211> 2247

<212> DNA

<213> Homo sapiens

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<222> (1)..(2244)

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 1 5 10 15

ctg gtc atc aat gta gga gaa gtg act ctt gga gaa gaa aac aga aaa 96
 Leu Val Ile Asn Val Gly Glu Val Thr Leu Gly Glu Glu Asn Arg Lys
 20 25 30

aag ctg cag aaa att cag aga gac caa gag aag gag aga gtt atg cgg 144
 Lys Leu Gln Lys Ile Gln Arg Asp Gln Glu Lys Glu Arg Val Met Arg
 35 40 45

gct gca tgt gct tta tta aac tca gga gga gga gtg att cga atg gcc 192
 Ala Ala Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Arg Met Ala
 50 55 60

aag aag gtt gag cat ccc gtg gag atg gga ctg gat tta gaa cag tct 240
 Lys Lys Val Glu His Pro Val Glu Met Gly Leu Asp Leu Glu Gln Ser
 65 70 75 80

ttg aga gag ctt att cag tct tca gat ctg cag gct ttc ttt gag acc 288
 Leu Arg Glu Leu Ile Gln Ser Ser Asp Leu Gln Ala Phe Phe Glu Thr
 85 90 95

aag caa caa gga agg tgt ttt tac att ttt gtt aaa tct tgg agc agt 336
 Lys Gln Gln Gly Arg Cys Phe Tyr Ile Phe Val Lys Ser Trp Ser Ser
 100 105 110

ggc cct ttc cct gaa gat cgc tct gtc aag ccc cgc ctt tgc agc ctc 384
 Gly Pro Phe Pro Glu Asp Arg Ser Val Lys Pro Arg Leu Cys Ser Leu
 115 120 125

agt tct tca tta tac cgt aga tct gag acc tct gtg cgt tcc atg gac 432
 Ser Ser Ser Leu Tyr Arg Arg Ser Glu Thr Ser Val Arg Ser Met Asp
 130 135 140

tca aga gag gca ttc tgt ttc ctg aag acc aaa agg aag cca aaa atc 480
 Ser Arg Glu Ala Phe Cys Phe Leu Lys Thr Lys Arg Lys Pro Lys Ile
 145 150 155 160

ttg gaa gaa gga cct ttt cac aaa att cac aag ggt gta tac caa gag 528
 Leu Glu Glu Gly Pro Phe His Lys Ile His Lys Gly Val Tyr Gln Glu
 165 170 175

ctc cct aac tcg gat cct gct gac cca aac tcg gat cct gct gac cta 576
 Leu Pro Asn Ser Asp Pro Ala Asp Pro Asn Ser Asp Pro Ala Asp Leu
 180 185 190

att ttc caa aaa gac tat ctt gaa tat ggt gaa atc ctg cct ttt cct 624
 Ile Phe Gln Lys Asp Tyr Leu Glu Tyr Gly Glu Ile Leu Pro Phe Pro
 195 200 205

gag tct cag tta gta gag ttt aaa cag ttc tct aca aaa cac ttc caa 672
 Glu Ser Gln Leu Val Glu Phe Lys Gln Phe Ser Thr Lys His Phe Gln
 210 215 220

82

gaa tat gta aaa agg aca att cca gaa tac gtc cct gca ttt gca aac Glu Tyr Val Lys Arg Thr Ile Pro Glu Tyr Val Pro Ala Phe Ala Asn 225 230 235 240	720
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aaa ata gaa can gcc ata tac aaa cta cct tgt ntt cat ttt tgc caa Lys Ile Glu Thr Ala Ile Tyr Lys Leu Pro Cys Xaa His Phe Cys Gln 275 280 285	864
ccc caa cgc ccg ata acc ttc aca ctc aaa att gtg gat gtn tta aaa Pro Gln Arg Pro Ile Thr Phe Thr Leu Lys Ile Val Asp Val Leu Lys 290 295 300	912
agg gga gag ctc tat ggc tat gct tgc atg atc aga gta aat ccc ttc Arg Gly Glu Leu Tyr Gly Tyr Ala Cys Met Ile Arg Val Asn Pro Phe 305 310 315 320	960
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ctg agt cta tct agt ggg cct ccc ctt agc aga cca gtg tac tcc aag Leu Ser Leu Ser Ser Gly Pro Pro Leu Ser Arg Pro Val Tyr Ser Lys 370 375 380	1152
aaa ggc ctg gaa cat aaa aag gaa ctc cag caa ctt tta ttt tca gtc Lys Gly Leu Glu His Lys Lys Glu Leu Gln Gln Leu Leu Phe Ser Val 385 390 395 400	1200
cca cca gga tat ttg cga tat act cca gag tca ctc tgg agg gac ctg Pro Pro Gly Tyr Leu Arg Tyr Thr Pro Glu Ser Leu Trp Arg Asp Leu 405 410 415	1248
atc tca gag cac aga gga cta gag gag tta ata aat aag caa atg caa Ile Ser Glu His Arg Gly Leu Glu Glu Leu Ile Asn Lys Gln Met Gln 420 425 430	1296
cct ttc ttt cgg gga att gtg atc ctc tct aga agc tgg gct gtg gac Pro Phe Phe Arg Gly Ile Val Ile Leu Ser Arg Ser Trp Ala Val Asp 435 440 445	1344
ctg aac ttg cag gag aag cca gga gtc atc tgt gat gct ctg ctg ata Leu Asn Leu Gln Glu Lys Pro Gly Val Ile Cys Asp Ala Leu Leu Ile 450 455 460	1392

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Ala Gln Asn Ser Thr Pro Ile Leu Tyr Thr Ile Leu Arg Glu Gln Asp	
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gca gag ggc cag gac tac tgc act cgc acc gcc ttt act ttg aag cag	1488
Ala Glu Gly Gln Asp Tyr Cys Thr Arg Thr Ala Phe Thr Leu Lys Gln	
485 490 495	
aag cta gtg aac atg ggg ggc tac acc ggg aag gtg tgt gtc agg gcc	1536
Lys Leu Val Asn Met Gly Gly Tyr Thr Gly Lys Val Cys Val Arg Ala	
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aag gtc ctc tgc ctg agt cct gag agc agc gca gag gcc ttg gag gct	1584
Lys Val Leu Cys Leu Ser Pro Glu Ser Ser Ala Glu Ala Leu Glu Ala	
515 520 525	
gca gtg tct ccg atg gat tac cct gcg tcc tat agc ctt gca ggc acc	1632
Ala Val Ser Pro Met Asp Tyr Pro Ala Ser Tyr Ser Leu Ala Gly Thr	
530 535 540	
cag cac atg gaa gcc ctg ctg cag tcc ctc gtg att gtc tta ctc ggc	1680
Gln His Met Glu Ala Leu Leu Gln Ser Leu Val Ile Val Leu Leu Gly	
545 550 555 560	
ttc agg tct ctc ttg agt gac cag ctc ggc tgt gag gtt tta aat ctg	1728
Phe Arg Ser Leu Leu Ser Asp Gln Leu Gly Cys Glu Val Leu Asn Leu	
565 570 575	
ctc aca gcc cag cag tat gag ata ttc tcc aga agc ctc cgc aag aac	1776
Leu Thr Ala Gln Gln Tyr Glu Ile Phe Ser Arg Ser Leu Arg Lys Asn	
580 585 590	
aga gag ttg ttt gtc cac ggc tta cct ggc tca ggg aag acc atc atg	1824
Arg Glu Leu Phe Val His Gly Leu Pro Gly Ser Gly Lys Thr Ile Met	
595 600 605	
gcc atg aag atc atg gag aag atc agg aat gtg ttt cac tgt gag gca	1872
Ala Met Lys Ile Met Glu Lys Ile Arg Asn Val Phe His Cys Glu Ala	
610 615 620	
cac aga att ctc tac gtt tgt gaa aac cag cct ctg agg aac ttt atc	1920
His Arg Ile Leu Tyr Val Cys Glu Asn Gln Pro Leu Arg Asn Phe Ile	
625 630 635 640	
agt gat aga aat atc tgc cga gca gag acc cgg aaa act ttc cta aga	1968
Ser Asp Arg Asn Ile Cys Arg Ala Glu Thr Arg Lys Thr Phe Leu Arg	
645 650 655	
gaa aac ttt gaa cac att caa cac atc gtc att gac gaa gct cag aat	2016
Glu Asn Phe Glu His Ile Gln His Ile Val Ile Asp Glu Ala Gln Asn	
660 665 670	
ttc cgt act gaa gat ggg gac tgg tat ggg aag gca aaa agc atc act	2064
Phe Arg Thr Glu Asp Gly Asp Trp Tyr Gly Lys Ala Lys Ser Ile Thr	
675 680 685	
cgg aga gca aag ggt ggc cca gga att ctc tgg atc ttt ctg gat tac	2112
Arg Arg Ala Lys Gly Gly Pro Gly Ile L u Trp Ile Phe Leu Asp Tyr	

84

690	695	700	
ttt cag acc agc cac ttg gat tgc agt ggc ctc cct cct ctc tca gac			2160
Phe Gln Thr Ser His Leu Asp Cys Ser Gly Leu Pro Pro Leu Ser Asp			
705	710	715	720
caa tat cca aga gaa gag ctc acc aga ata gtt cgc aat gca gat cca			2208
Gln Tyr Pro Arg Glu Glu Leu Thr Arg Ile Val Arg Asn Ala Asp Pro			
	725	730	735
ata gcc aag tac tta caa aaa gaa aat gca agt aat tag			2247
Ile Ala Lys Tyr Leu Gln Lys Glu Asn Ala Ser Asn			
	740	745	

<210> 43

<211> 748

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (248)..(248)

<223> The 'Xaa' at location 248 stands for Ile, Val, Leu, or Phe.

<220>

<221> misc_feature

<222> (265)..(265)

<223> The 'Xaa' at location 265 stands for Ile, Val, Leu, or Phe.

<220>

<221> misc_feature

<222> (272)..(272)

<223> The 'Xaa' at location 272 stands for Arg, Gly, or Trp.

<220>

<221> misc_feature

<222> (284)..(284)

<223> The 'Xaa' at location 284 stands for Ile, Val, Leu, or Phe.

<220>

85

<221> misc_feature
<222> (742)..(742)
<223> unknown amino
<220>
<221> misc_feature
<222> (747)..(747)
<223> unknown amino
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<222> (793)..(793)
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<222> (814)..(814)
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<221> misc_feature
<222> (828)..(828)
<223> unknown amino
<220>
<221> misc_feature
<222> (850)..(850)
<223> unknown amino
<220>
<221> misc_feature
<222> (906)..(906)
<223> unknown amino
<400> 43

Met Glu Ala Asn Gln Cys Pro Leu Val Val Glu Pro Ser Tyr Pro Asp
1 5 10 15

86

Leu Val Ile Asn Val Gly Glu Val Thr Leu Gly Glu Glu Asn Arg Lys
 20 25 30

Lys Leu Gln Lys Ile Gln Arg Asp Gln Glu Lys Glu Arg Val Met Arg
 35 40 45

Ala Ala Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Arg Met Ala
 50 55 60

Lys Lys Val Glu His Pro Val Glu Met Gly Leu Asp Leu Glu Gln Ser
 65 70 75 80

Leu Arg Glu Leu Ile Gln Ser Ser Asp Leu Gln Ala Phe Phe Glu Thr
 85 90 95

Lys Gln Gln Gly Arg Cys Phe Tyr Ile Phe Val Lys Ser Trp Ser Ser
 100 105 110

Gly Pro Phe Pro Glu Asp Arg Ser Val Lys Pro Arg Leu Cys Ser Leu
 115 120 125

Ser Ser Ser Leu Tyr Arg Arg Ser Glu Thr Ser Val Arg Ser Met Asp
 130 135 140

Ser Arg Glu Ala Phe Cys Phe Leu Lys Thr Lys Arg Lys Pro Lys Ile
 145 150 155 160

Leu Glu Glu Gly Pro Phe His Lys Ile His Lys Gly Val Tyr Gln Glu
 165 170 175

Leu Pro Asn Ser Asp Pro Ala Asp Pro Asn Ser Asp Pro Ala Asp Leu
 180 185 190

Ile Phe Gln Lys Asp Tyr Leu Glu Tyr Gly Glu Ile Leu Pro Phe Pro
 195 200 205

Glu Ser Gln Leu Val Glu Phe Lys Gln Phe Ser Thr Lys His Phe Gln
 210 215 220

Glu Tyr Val Lys Arg Thr Ile Pro Glu Tyr Val Pro Ala Phe Ala Asn
 225 230 235 240

Thr Gly Gly Gly Tyr Leu Phe Xaa Gly Val Asp Asp Lys Ser Arg Glu
 245 250 255

Val Leu Gly Cys Ala Lys Glu Asn Xaa Asp Pro Asp Ser Leu Arg Xaa
 260 265 270

Lys Ile Glu Thr Ala Ile Tyr Lys Leu Pro Cys Xaa His Phe Cys Gln
 275 280 285

Pro Gln Arg Pro Ile Thr Phe Thr Leu Lys Ile Val Asp Val Leu Lys
 290 295 300

Arg Gly Glu Leu Tyr Gly Tyr Ala Cys Met Ile Arg Val Asn Pro Phe
 305 310 315 320

Cys Cys Ala Val Phe Ser Glu Ala Pro Asn Ser Trp Ile Val Glu Asp
 325 330 335

Lys Tyr Val Cys Ser Leu Thr Thr Glu Lys Trp Val Gly Met Met Thr
 340 345 350

Asp Thr Asp Pro Asp Leu Leu Gln Leu Ser Glu Asp Phe Glu Cys Gln
 355 360 365

Leu Ser Leu Ser Ser Gly Pro Pro Leu Ser Arg Pro Val Tyr Ser Lys
 370 375 380

Lys Gly Leu Glu His Lys Lys Glu Leu Gln Gln Leu Leu Phe Ser Val
 385 390 395 400

Pro Pro Gly Tyr Leu Arg Tyr Thr Pro Glu Ser Leu Trp Arg Asp Leu
 405 410 415

Ile Ser Glu His Arg Gly Leu Glu Glu Leu Ile Asn Lys Gln Met Gln
 420 425 430

Pro Phe Phe Arg Gly Ile Val Ile Leu Ser Arg Ser Trp Ala Val Asp
 435 440 445

Leu Asn Leu Gln Glu Lys Pro Gly Val Ile Cys Asp Ala Leu Leu Ile
 450 455 460

Ala Gln Asn Ser Thr Pro Ile Leu Tyr Thr Ile Leu Arg Glu Gln Asp
 465 470 475 480

Ala Glu Gly Gln Asp Tyr Cys Thr Arg Thr Ala Phe Thr Leu Lys Gln

485

495

Phe Gln Thr Ser His Leu Asp Cys Ser Gly Leu Pro Pro Leu Ser Asp
705 710 715 720

89

Gln Tyr Pro Arg Glu Glu Leu Thr Arg Ile Val Arg Asn Ala Asp Pro
 725 730 735

Ile Ala Lys Tyr Leu Gln Lys Glu Asn Ala Ser Asn
 740 745

<210> 44

<211> 2676

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1) .. (2673)

<223>

<400> 44

atg agt ctt agg att gat gtg gat aca aac ttt cct gag tgt gtt gta 48
 Met Ser Leu Arg Ile Asp Val Asp Thr Asn Phe Pro Glu Cys Val Val
 1 5 10 15

gat gca gga aaa gtc acc ctt ggg act cag cag agg cag gag atg gac 96
 Asp Ala Gly Lys Val Thr Leu Gly Thr Gln Gln Arg Gln Glu Met Asp
 20 25 30

cct cgc ctg cgg gag aaa cag aat gaa atc atc ctg cga gca gta tgt 144
 Pro Arg Leu Arg Glu Lys Gln Asn Glu Ile Ile Leu Arg Ala Val Cys
 35 40 45

gct ctg ctg aat tct ggt ggg ggc ata atc aag gct gag att gag aac 192
 Ala Leu Leu Asn Ser Gly Gly Gly Ile Ile Lys Ala Glu Ile Glu Asn
 50 55 60

aaa ggc tac aat tat gaa cgt cat gga gta gga ttg gat gtg cct cca 240
 Lys Gly Tyr Asn Tyr Glu Arg His Gly Val Gly Leu Asp Val Pro Pro
 65 70 75 80

att ttc aga agc cat tta gat aag atg cag aag gaa aac cac ttt ttg 288
 Ile Phe Arg Ser His Leu Asp Lys Met Gln Lys Glu Asn His Phe Leu
 85 90 95

att ttt gtg aaa tca tgg aac aca gag gct ggt gtg cca ctt gct acc 336
 Ile Phe Val Lys Ser Trp Asn Thr Glu Ala Gly Val Pro Leu Ala Thr
 100 105 110

tta tgc tcc aat ttg tac cac aga gag aga aca tcc acc gat gtc atg 384
 Leu Cys Ser Asn Leu Tyr His Arg Glu Arg Thr Ser Thr Asp Val Met

90

115	120	125	
gat tct cag gaa gct ctg gca ttc ctc aaa tgc agg act cag act cca			432
Asp Ser Gln Glu Ala Leu Ala Phe Leu Lys Cys Arg Thr Gln Thr Pro			
130	135	140	
acg aat att aat gtt tcc aat tca tta ggt cca cag gca gct cag ggt			480
Thr Asn Ile Asn Val Ser Asn Ser Leu Gly Pro Gln Ala Ala Gln Gly			
145	150	155	160
agt gta caa tat gaa ggt aac ata aat gtg tca gct gct gct tta ttt			528
Ser Val Gln Tyr Glu Gly Asn Ile Asn Val Ser Ala Ala Ala Leu Phe			
165	170	175	
gat aga aag cgg ctt cag tat ctg gaa aaa ctc aac ctt cct gag tcc			576
Asp Arg Lys Arg Leu Gln Tyr Leu Glu Lys Leu Asn Leu Pro Glu Ser			
180	185	190	
aca cat gtt gaa ttt gta atg ttc tcg aca gac gtg tca cac tgt gtt			624
Thr His Val Glu Phe Val Met Phe Ser Thr Asp Val Ser His Cys Val			
195	200	205	
aaa gac aga ctt ccg aag tgt gtt tct gca ttt gca aat act gaa gga			672
Lys Asp Arg Leu Pro Lys Cys Val Ser Ala Phe Ala Asn Thr Glu Gly			
210	215	220	
gga tat gta ttt ttt ggt gtg cat gat gag act tgt caa gtg att gga			720
Gly Tyr Val Phe Phe Gly Val His Asp Glu Thr Cys Gln Val Ile Gly			
225	230	235	240
tgt gaa aaa gag aaa ata gac ctt acg agc ttg agg gct tct att gat			768
Cys Glu Lys Glu Lys Ile Asp Leu Thr Ser Leu Arg Ala Ser Ile Asp			
245	250	255	
ggc tgt att aag aag cta cct gtc cat cat ttc tgc aca cag agg cct			816
Gly Cys Ile Lys Lys Leu Pro Val His His Phe Cys Thr Gln Arg Pro			
260	265	270	
gag ata aaa tat gtc ctt aac ttc ctt gaa gtg cat gat aag ggg gcc			864
Glu Ile Lys Tyr Val Leu Asn Phe Leu Glu Val His Asp Lys Gly Ala			
275	280	285	
ctc cgt gga tat gtc tgt gca atc aag gtg gag aaa ttc tgc tgt gcg			912
Leu Arg Gly Tyr Val Cys Ala Ile Lys Val Glu Lys Phe Cys Cys Ala			
290	295	300	
gtg ttt gcc aaa gtg cct agt tcc tgg cag gtg aag gac aac cgt gtg			960
Val Phe Ala Lys Val Pro Ser Ser Trp Gln Val Lys Asp Asn Arg Val			
305	310	315	320
aga caa ttg ccc aca aga gaa tgg act gct tgg atg atg gaa gct gac			1008
Arg Gln Leu Pro Thr Arg Glu Trp Thr Ala Trp Met Met Glu Ala Asp			
325	330	335	
cca gac ctt tcc agg tgt cct gag atg gtt ctc cag ttg agt ttg tca			1056
Pro Asp Leu Ser Arg Cys Pro Glu Met Val Leu Gln Leu Ser Leu Ser			
340	345	350	
tct gcc acg ccc cgc agc aag cct gtg tgc att cat aag aat tcg gaa			1104

91

Ser	Ala	Thr	Pro	Arg	Ser	Lys	Pro	Val	Cys	Ile	His	Lys	Asn	Ser	Glu		
		355					360					365					
tgt	ctg	aaa	gag	cag	cag	aaa	cgc	tac	ttt	cca	gta	ttt	tca	gac	aga		1152
Cys	Leu	Lys	Glu	Gln	Gln	Lys	Arg	Tyr	Phe	Pro	Val	Phe	Ser	Asp	Arg		
	370					375				380							
gtg	gta	tat	act	cca	gaa	agc	ctc	tac	aag	gaa	ctc	ttc	tca	caa	cat		1200
Val	Val	Tyr	Thr	Pro	Glu	Ser	Leu	Tyr	Lys	Glu	Leu	Phe	Ser	Gln	His		
	385				390					395					400		
aaa	gga	ctc	aga	gac	tta	ata	aat	aca	gaa	atg	cgc	cct	ttc	tct	caa		1248
Lys	Gly	Leu	Arg	Asp	Leu	Ile	Asn	Thr	Glu	Met	Arg	Pro	Phe	Ser	Gln		
				405					410						415		
gga	ata	ttg	att	ttt	tct	caa	agc	tgg	gct	gtg	gat	tta	ggg	ctg	caa		1296
Gly	Ile	Leu	Ile	Phe	Ser	Gln	Ser	Trp	Ala	Val	Asp	Leu	Gly	Leu	Gln		
			420					425					430				
gag	aag	cag	gga	gtc	atc	tgt	gat	gct	ctt	cta	att	tcc	cag	aac	aac		1344
Glu	Lys	Gln	Gly	Val	Ile	Cys	Asp	Ala	Leu	Leu	Ile	Ser	Gln	Asn	Asn		
		435					440						445				
acc	cct	att	ctc	tac	acc	atc	ttc	agc	aag	tgg	gat	gcg	ggg	tgc	aag		1392
Thr	Pro	Ile	Leu	Tyr	Thr	Ile	Phe	Ser	Lys	Trp	Asp	Ala	Gly	Cys	Lys		
		450				455					460						
ggc	tat	tct	atg	ata	gtt	gcc	tat	tct	ttg	aag	cag	aag	ctg	gtg	aac		1440
Gly	Tyr	Ser	Met	Ile	Val	Ala	Tyr	Ser	Leu	Lys	Gln	Lys	Leu	Val	Asn		
	465				470					475					480		
aaa	ggc	ggc	tac	act	ggg	agg	tta	tgc	atc	acc	ccc	ttg	gtc	tgt	gtg		1488
Lys	Gly	Gly	Tyr	Thr	Gly	Arg	Leu	Cys	Ile	Thr	Pro	Leu	Val	Cys	Val		
				485					490					495			
ctg	aat	tct	gat	aga	aaa	gca	cag	agc	gtt	tac	agt	tcg	tat	tta	caa		1536
Leu	Asn	Ser	Asp	Arg	Lys	Ala	Gln	Ser	Val	Tyr	Ser	Ser	Tyr	Leu	Gln		
			500					505					510				
att	tac	cct	gaa	tcc	tat	aac	ttc	atg	acc	ccc	cag	cac	atg	gaa	gcc		1584
Ile	Tyr	Pro	Glu	Ser	Tyr	Asn	Phe	Met	Thr	Pro	Gln	His	Met	Glu	Ala		
		515					520					525					
ctg	tta	cag	tcc	ctc	gtg	ata	gtc	ttg	ctt	ggg	ttc	aaa	tcc	ttc	tta		1632
Leu	Leu	Gln	Ser	Leu	Val	Ile	Val	Leu	Leu	Gly	Phe	Lys	Ser	Phe	Leu		
		530				535					540						
agt	gaa	gag	ctg	ggc	tct	gag	gtt	ttg	aac	cta	ctg	aca	aat	aaa	cag		1680
Ser	Glu	Glu	Leu	Gly	Ser	Glu	Val	Leu	Asn	Leu	Leu	Thr	Asn	Lys	Gln		
	545				550					555					560		
tat	gag	ttg	ctt	tca	aag	aac	ctt	cgc	aag	acc	aga	gag	ttg	ttt	gtt		1728
Tyr	Glu	Leu	Leu	Ser	Lys	Asn	Leu	Arg	Lys	Thr	Arg	Glu	Leu	Phe	Val		
			565					570						575			
cat	ggc	tta	cct	gga	tca	ggg	aag	act	atc	ttg	gct	ctt	agg	atc	atg		1776
His	Gly	Leu	Pro	Gly	Ser	Gly	Lys	Thr	Ile	Leu	Ala	Leu	Arg	Ile	Met		
			580					585					590				

gag aag atc agg aat gtg ttt cac tgt gaa ccg gct aac att ctc tac	1824
Glu Lys Ile Arg Asn Val Phe His Cys Glu Pro Ala Asn Ile Leu Tyr	
595 600 605	
atc tgt gaa aac cag ccc ctg aag aag ttg gtg agt ttc agc aag aaa	1872
Ile Cys Glu Asn Gln Pro Leu Lys Lys Leu Val Ser Phe Ser Lys Lys	
610 615 620	
aac atc tgc cag cca gtg acc cgg aaa acc ttc atg aaa aac aac ttt	1920
Asn Ile Cys Gln Pro Val Thr Arg Lys Thr Phe Met Lys Asn Asn Phe	
625 630 635 640	
gaa cac atc cag cac att atc att gat gac gct cag aat ttc cgt act	1968
Glu His Ile Gln His Ile Ile Ile Asp Ala Gln Asn Phe Arg Thr	
645 650 655	
gaa gat ggg gac tgg tat ggg aaa gca aag ttc atc act cga cag caa	2016
Glu Asp Gly Asp Trp Tyr Gly Lys Ala Lys Phe Ile Thr Arg Gln Gln	
660 665 670	
agg gat ggc cca gga gtt ctc tgg atc ttt ctg gac tac ttt cag acc	2064
Arg Asp Gly Pro Gly Val Leu Trp Ile Phe Leu Asp Tyr Phe Gln Thr	
675 680 685	
tat cac ttg agt tgc agt ggc ctc ccc cct ccc tca gac cag tat cca	2112
Tyr His Leu Ser Cys Ser Gly Leu Pro Pro Pro Ser Asp Gln Tyr Pro	
690 695 700	
aga gaa gag atc aac aga gtg gtc cgc aat gca ggt cca ata gct aat	2160
Arg Glu Glu Ile Asn Arg Val Val Arg Asn Ala Gly Pro Ile Ala Asn	
705 710 715 720	
tac cta caa caa gta atg cag gaa gcc cga caa aat cct cca cct aac	2208
Tyr Leu Gln Gln Val Met Gln Glu Ala Arg Gln Asn Pro Pro Pro Asn	
725 730 735	
ctc ccc cct ggg tcc ctg gtg atg ctc tat gaa cct aaa tgg gct caa	2256
Leu Pro Pro Gly Ser Leu Val Met Leu Tyr Glu Pro Lys Trp Ala Gln	
740 745 750	
ggt gtc cca ggc aac tta gag att att gaa gac ttg aac ttg gag gag	2304
Gly Val Pro Gly Asn Leu Glu Ile Ile Glu Asp Leu Asn Leu Glu Glu	
755 760 765	
ata ctg atc tat gta gcg aat aaa tgc cgt ttt ctc ttg cgg aat ggt	2352
Ile Leu Ile Tyr Val Ala Asn Lys Cys Arg Phe Leu Leu Arg Asn Gly	
770 775 780	
tat tct ccg aag gat att gct gtg ctt ttc acc aaa gca agt gaa gtg	2400
Tyr Ser Pro Lys Asp Ile Ala Val Leu Phe Thr Lys Ala Ser Glu Val	
785 790 795 800	
gaa aaa tat aaa gac agg ctt cta aca gca atg agg aag aga aaa ctg	2448
Glu Lys Tyr Lys Asp Arg Leu Leu Thr Ala Met Arg Lys Arg Lys Leu	
805 810 815	
tct cag ctc cat gag gag tct gat ctg tta cta cag atc ggt gat gcg	2496
Ser Gln Leu His Glu Glu Ser Asp Leu Leu Leu Gln Ile Gly Asp Ala	
820 825 830	

93

tcg gat gtt cta acc gat cac att gtg ttg gac agt gtc tgt cga ttt 2544
 Ser Asp Val Leu Thr Asp His Ile Val Leu Asp Ser Val Cys Arg Phe
 835 840 845

tca ggc ctg gaa aga aat atc gtg ttt gga atc aat cca gga gta gcc 2592
 Ser Gly Leu Glu Arg Asn Ile Val Phe Gly Ile Asn Pro Gly Val Ala
 850 855 860

cca ccg gct ggg gcc tac aat ctt ctg ctc tgt ttg gct tct agg gca 2640
 Pro Pro Ala Gly Ala Tyr Asn Leu Leu Leu Cys Leu Ala Ser Arg Ala
 865 870 875 880

aaa aga cat ctg tat att ctg aag gct tct gtg tga 2676
 Lys Arg His Leu Tyr Ile Leu Lys Ala Ser Val
 885 890

<210> 45

<211> 891

<212> PRT

<213> Homo sapiens

<400> 45

Met Ser Leu Arg Ile Asp Val Asp Thr Asn Phe Pro Glu Cys Val Val
 1 5 10 15

Asp Ala Gly Lys Val Thr Leu Gly Thr Gln Gln Arg Gln Glu Met Asp
 20 25 30

Pro Arg Leu Arg Glu Lys Gln Asn Glu Ile Ile Leu Arg Ala Val Cys
 35 40 45

Ala Leu Leu Asn Ser Gly Gly Gly Ile Ile Lys Ala Glu Ile Glu Asn
 50 55 60

Lys Gly Tyr Asn Tyr Glu Arg His Gly Val Gly Leu Asp Val Pro Pro
 65 70 75 80

Ile Phe Arg Ser His Leu Asp Lys Met Gln Lys Glu Asn His Phe Leu
 85 90 95

Ile Phe Val Lys Ser Trp Asn Thr Glu Ala Gly Val Pro Leu Ala Thr
 100 105 110

Leu Cys Ser Asn Leu Tyr His Arg Glu Arg Thr Ser Thr Asp Val Met

94

115	120	125
Asp Ser Gln Glu Ala Leu Ala Phe Leu Lys Cys Arg Thr Gln Thr Pro		
130	135	140
Thr Asn Ile Asn Val Ser Asn Ser Leu Gly Pro Gln Ala Ala Gln Gly		
145	150	155
		160
Ser Val Gln Tyr Glu Gly Asn Ile Asn Val Ser Ala Ala Ala Leu Phe		
	165	170
		175
Asp Arg Lys Arg Leu Gln Tyr Leu Glu Lys Leu Asn Leu Pro Glu Ser		
	180	185
		190
Thr His Val Glu Phe Val Met Phe Ser Thr Asp Val Ser His Cys Val		
	195	200
		205
Lys Asp Arg Leu Pro Lys Cys Val Ser Ala Phe Ala Asn Thr Glu Gly		
	210	215
		220
Gly Tyr Val Phe Phe Gly Val His Asp Glu Thr Cys Gln Val Ile Gly		
	225	230
		235
		240
Cys Glu Lys Glu Lys Ile Asp Leu Thr Ser Leu Arg Ala Ser Ile Asp		
	245	250
		255
Gly Cys Ile Lys Lys Leu Pro Val His His Phe Cys Thr Gln Arg Pro		
	260	265
		270
Glu Ile Lys Tyr Val Leu Asn Phe Leu Glu Val His Asp Lys Gly Ala		
	275	280
		285
Leu Arg Gly Tyr Val Cys Ala Ile Lys Val Glu Lys Phe Cys Cys Ala		
	290	295
		300
Val Phe Ala Lys Val Pro Ser Ser Trp Gln Val Lys Asp Asn Arg Val		
	305	310
		315
		320
Arg Gln Leu Pro Thr Arg Glu Trp Thr Ala Trp Met Met Glu Ala Asp		
	325	330
		335
Pro Asp Leu Ser Arg Cys Pro Glu Met Val Leu Gln Leu Ser Leu Ser		
	340	345
		350

95

Ser Ala Thr Pro Arg Ser Lys Pro Val Cys Ile His Lys Asn Ser Glu
 355 360 365

Cys Leu Lys Glu Gln Gln Lys Arg Tyr Phe Pro Val Phe Ser Asp Arg
 370 375 380

Val Val Tyr Thr Pro Glu Ser Leu Tyr Lys Glu Leu Phe Ser Gln His
 385 390 395 400

Lys Gly Leu Arg Asp Leu Ile Asn Thr Glu Met Arg Pro Phe Ser Gln
 405 410 415

Gly Ile Leu Ile Phe Ser Gln Ser Trp Ala Val Asp Leu Gly Leu Gln
 420 425 430

Glu Lys Gln Gly Val Ile Cys Asp Ala Leu Leu Ile Ser Gln Asn Asn
 435 440 445

Thr Pro Ile Leu Tyr Thr Ile Phe Ser Lys Trp Asp Ala Gly Cys Lys
 450 455 460

Gly Tyr Ser Met Ile Val Ala Tyr Ser Leu Lys Gln Lys Leu Val Asn
 465 470 475 480

Lys Gly Gly Tyr Thr Gly Arg Leu Cys Ile Thr Pro Leu Val Cys Val
 485 490 495

Leu Asn Ser Asp Arg Lys Ala Gln Ser Val Tyr Ser Ser Tyr Leu Gln
 500 505 510

Ile Tyr Pro Glu Ser Tyr Asn Phe Met Thr Pro Gln His Met Glu Ala
 515 520 525

Leu Leu Gln Ser Leu Val Ile Val Leu Leu Gly Phe Lys Ser Phe Leu
 530 535 540

Ser Glu Glu Leu Gly Ser Glu Val Leu Asn Leu Leu Thr Asn Lys Gln
 545 550 555 560

Tyr Glu Leu Leu Ser Lys Asn Leu Arg Lys Thr Arg Glu Leu Phe Val
 565 570 575

His Gly Leu Pro Gly Ser Gly Lys Thr Ile Leu Ala Leu Arg Ile Met
 580 585 590

Glu Lys Ile Arg Asn Val Phe His Cys Glu Pro Ala Asn Ile Leu Tyr
 595 600 605

Ile Cys Glu Asn Gln Pro Leu Lys Lys Leu Val Ser Phe Ser Lys Lys
 610 615 620

Asn Ile Cys Gln Pro Val Thr Arg Lys Thr Phe Met Lys Asn Asn Phe
 625 630 635 640

Glu His Ile Gln His Ile Ile Ile Asp Asp Ala Gln Asn Phe Arg Thr
 645 650 655

Glu Asp Gly Asp Trp Tyr Gly Lys Ala Lys Phe Ile Thr Arg Gln Gln
 660 665 670

Arg Asp Gly Pro Gly Val Leu Trp Ile Phe Leu Asp Tyr Phe Gln Thr
 675 680 685

Tyr His Leu Ser Cys Ser Gly Leu Pro Pro Pro Ser Asp Gln Tyr Pro
 690 695 700

Arg Glu Glu Ile Asn Arg Val Val Arg Asn Ala Gly Pro Ile Ala Asn
 705 710 715 720

Tyr Leu Gln Gln Val Met Gln Glu Ala Arg Gln Asn Pro Pro Pro Asn
 725 730 735

Leu Pro Pro Gly Ser Leu Val Met Leu Tyr Glu Pro Lys Trp Ala Gln
 740 745 750

Gly Val Pro Gly Asn Leu Glu Ile Ile Glu Asp Leu Asn Leu Glu Glu
 755 760 765

Ile Leu Ile Tyr Val Ala Asn Lys Cys Arg Phe Leu Leu Arg Asn Gly
 770 775 780

Tyr Ser Pro Lys Asp Ile Ala Val Leu Phe Thr Lys Ala Ser Glu Val
 785 790 795 800

Glu Lys Tyr Lys Asp Arg Leu Leu Thr Ala Met Arg Lys Arg Lys Leu
 805 810 815

Ser Gln Leu His Glu Glu Ser Asp Leu Leu Leu Gln Ile Gly Asp Ala
 820 825 830

97

Ser Asp Val Leu Thr Asp His Ile Val Leu Asp Ser Val Cys Arg Phe
 835 840 845

Ser Gly Leu Glu Arg Asn Ile Val Phe Gly Ile Asn Pro Gly Val Ala
 850 855 860

Pro Pro Ala Gly Ala Tyr Asn Leu Leu Leu Cys Leu Ala Ser Arg Ala
 865 870 875 880

Lys Arg His Leu Tyr Ile Leu Lys Ala Ser Val
 885 890

<210> 46

<211> 1737

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(1734)

<223>

<400> 46
 atg aac atc agt gtt gat ttg gaa acg aat tat gcc gag ttg gtt cta 48
 Met Asn Ile Ser Val Asp Leu Glu Thr Asn Tyr Ala Glu Leu Val Leu
 1 5 10 15
 gat gtg gga aga gtc act ctt gga gag aac agt agg aaa aaa atg aag 96
 Asp Val Gly Arg Val Thr Leu Gly Glu Asn Ser Arg Lys Lys Met Lys
 20 25 30
 gat tgt aaa ctg aga aaa aag cag aat gaa agg gtc tca cga gct atg 144
 Asp Cys Lys Leu Arg Lys Lys Gln Asn Glu Arg Val Ser Arg Ala Met
 35 40 45
 tgt gct ctg ctc aat tct gga ggg gga gtg atc aag gct gaa att gag 192
 Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Lys Ala Glu Ile Glu
 50 55 60
 aat gaa gac tat agt tat aca aaa gat gga ata gga cta gat ttg gaa 240
 Asn Glu Asp Tyr Ser Tyr Thr Lys Asp Gly Ile Gly Leu Asp Leu Glu
 65 70 75 80

98

aat tct ttt agt aac att ctg tta ttt gtt cct gag tac tta gac ttc Asn Ser Phe Ser Asn Ile Leu Leu Phe Val Pro Glu Tyr Leu Asp Phe	288
85 90 95	
atg cag aat ggt aac tac ttt ctg att ttt gtg aag tca tgg agc ttg Met Gln Asn Gly Asn Tyr Phe Leu Ile Phe Val Lys Ser Trp Ser Leu	336
100 105 110	
aac acc tct ggt ctg cgg att acc acc ttg agc tcc aat ttg tac aaa Asn Thr Ser Gly Leu Arg Ile Thr Thr Leu Ser Ser Asn Leu Tyr Lys	384
115 120 125	
aga gat ata aca tct gca aaa gtc atg aat gcc act gct gca ctg gag Arg Asp Ile Thr Ser Ala Lys Val Met Asn Ala Thr Ala Ala Leu Glu	432
130 135 140	
ttc ctc aaa gac atg aaa aag act aga ggg aga ttg tat tta aga cca Phe Leu Lys Asp Met Lys Lys Thr Arg Gly Arg Leu Tyr Leu Arg Pro	480
145 150 155 160	
gaa ttg ctg gca aag agg ccc tgt gtt gat ata caa gaa gaa aat aac Glu Leu Leu Ala Lys Arg Pro Cys Val Asp Ile Gln Glu Glu Asn Asn	528
165 170 175	
atg aag gcc ttg gcc ggg gtt ttt ttt gat aga aca gaa ctt gat cgg Met Lys Ala Leu Ala Gly Val Phe Phe Asp Arg Thr Glu Leu Asp Arg	576
180 185 190	
aaa gaa aaa ttg acc ttt act gaa tcc aca cat gtt gaa att aaa aac Lys Glu Lys Leu Thr Phe Thr Glu Ser Thr His Val Glu Ile Lys Asn	624
195 200 205	
ttc tcg aca gaa aag ttg tta caa cga att aaa gag att ctc cct caa Phe Ser Thr Glu Lys Leu Leu Gln Arg Ile Lys Glu Ile Leu Pro Gln	672
210 215 220	
tat gtt tct gca ttt gca aat act gat gga gga tat ttg ttc att ggt Tyr Val Ser Ala Phe Ala Asn Thr Asp Gly Gly Tyr Leu Phe Ile Gly	720
225 230 235 240	
tta aat gaa gat aaa gaa ata att ggc ttt aaa gca gag atg agt gac Leu Asn Glu Asp Lys Glu Ile Ile Gly Phe Lys Ala Glu Met Ser Asp	768
245 250 255	
ctc gat gac tta gaa aga gaa atc gaa aag tcc att agg aag atg cct Leu Asp Asp Leu Glu Arg Glu Ile Glu Lys Ser Ile Arg Lys Met Pro	816
260 265 270	
gtg cat cac ttc tgt atg gag aag aag aag ata aat tat tca tgc aaa Val His His Phe Cys Met Glu Lys Lys Lys Ile Asn Tyr Ser Cys Lys	864
275 280 285	
ttc ctt gga gta tat gat aaa gga agt ctt tgt gga tat gtc tgt gca Phe Leu Gly Val Tyr Asp Lys Gly Ser Leu Cys Gly Tyr Val Cys Ala	912
290 295 300	
ctc aga gtg gag cgc ttc tgc tgt gca gtg ttt gct aaa gag cct gat Leu Arg Val Glu Arg Phe Cys Cys Ala Val Phe Ala Lys Glu Pro Asp	960
305 310 315 320	

tcc tgg cat gtg aaa gat aac cgt gtg atg cag ttg acc agg aag gaa Ser Trp His Val Lys Asp Asn Arg Val Met Gln Leu Thr Arg Lys Glu 325 330 335	1008
tgg atc cag ttc atg gtg gag gct gaa cca aaa ttt tcc agt tca tat Trp Ile Gln Phe Met Val Glu Ala Glu Pro Lys Phe Ser Ser Ser Tyr 340 345 350	1056
gaa gag gtg atc tct caa ata aat acg tca tta cct gct ccc cac agt Glu Glu Val Ile Ser Gln Ile Asn Thr Ser Leu Pro Ala Pro His Ser 355 360 365	1104
tgg cct ctt ttg gaa tgg caa cgg cag aga cat cac tgt cca ggg cta Trp Pro Leu Leu Glu Trp Gln Arg Gln Arg His His Cys Pro Gly Leu 370 375 380	1152
tca gga agg ata acg tat act cca gaa aac ctt tgc aga aaa ctg ttc Ser Gly Arg Ile Thr Tyr Thr Pro Glu Asn Leu Cys Arg Lys Leu Phe 385 390 395 400	1200
tta caa cat gaa gga ctt aag caa tta ata tgt gaa gaa atg gac tct Leu Gln His Glu Gly Leu Lys Gln Leu Ile Cys Glu Glu Met Asp Ser 405 410 415	1248
gtc aga aag ggc tca ctg atc ttc tct agg agc tgg tct gtg gat ctg Val Arg Lys Gly Ser Leu Ile Phe Ser Arg Ser Trp Ser Val Asp Leu 420 425 430	1296
ggc ttg caa gag aac cac aaa gtc ctc tgt gat gct ctt ctg att tcc Gly Leu Gln Glu Asn His Lys Val Leu Cys Asp Ala Leu Leu Ile Ser 435 440 445	1344
cag gac agt cct cca gtc cta tac acc ttc cac atg gta cag gat gag Gln Asp Ser Pro Pro Val Leu Tyr Thr Phe His Met Val Gln Asp Glu 450 455 460	1392
gag ttt aaa ggc tat tct aca caa act gcc cta acc tta aag cag aag Glu Phe Lys Gly Tyr Ser Thr Gln Thr Ala Leu Thr Leu Lys Gln Lys 465 470 475 480	1440
ctg gca aaa att ggt ggt tac act aaa aaa gtg tgt gtc atg aca aag Leu Ala Lys Ile Gly Gly Tyr Thr Lys Lys Val Cys Val Met Thr Lys 485 490 495	1488
atc ttc tac ttg agc cct gaa ggc atg aca agc tgc cag tat gat tta Ile Phe Tyr Leu Ser Pro Glu Gly Met Thr Ser Cys Gln Tyr Asp Leu 500 505 510	1536
agg tgc caa gta att tac cct gaa tcc tac tat ttt aca aga agg aaa Arg Ser Gln Val Ile Tyr Pro Glu Ser Tyr Tyr Phe Thr Arg Arg Lys 515 520 525	1584
tac ttg ctg aaa gcc ctt ttt aaa gcc tta aag aga ctc aag tct ctg Tyr Leu Leu Lys Ala Leu Phe Lys Ala Leu Lys Arg Leu Lys Ser Leu 530 535 540	1632
aga gac cag ttt tcc ttt gca gaa aat cta tac cag ata atc ggt ata Arg Asp Gln Phe Ser Phe Ala Glu Asn Leu Tyr Gln Ile Ile Gly Ile	1680

[illegible]

<213> Homo sapiens

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Asp Cys Lys Leu Arg Lys Lys Gln Asn Glu Arg Val Ser Arg Ala Met
35 40 45

Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Lys Ala Glu Ile Glu
50 55 60

Asn Glu Asp Tyr Ser Tyr Thr Lys Asp Gly Ile Gly Leu Asp Leu Glu
65 70 75 80

Asn Ser Phe Ser Asn Ile Leu Leu Phe Val Pro Glu Tyr Leu Asp Phe
85 90 95

Met Gln Asn Gly Asn Tyr Phe Leu Ile Phe Val Lys Ser Trp Ser Leu
100 105 110

Asn Thr Ser Gly Leu Arg Ile Thr Thr Leu Ser Ser Asn Leu Tyr Lys
115 120 125

Arg Asp Ile Thr Ser Ala Lys Val Met Asn Ala Thr Ala Ala Leu Glu
130 135 140

101

Phe Leu Lys Asp Met Lys Lys Thr Arg Gly Arg Leu Tyr Leu Arg Pro
 145 150 155 160

Glu Leu Leu Ala Lys Arg Pro Cys Val Asp Ile Gln Glu Glu Asn Asn
 165 170 175

Met Lys Ala Leu Ala Gly Val Phe Phe Asp Arg Thr Glu Leu Asp Arg
 180 185 190

Lys Glu Lys Leu Thr Phe Thr Glu Ser Thr His Val Glu Ile Lys Asn
 195 200 205

Phe Ser Thr Glu Lys Leu Leu Gln Arg Ile Lys Glu Ile Leu Pro Gln
 210 215 220

Tyr Val Ser Ala Phe Ala Asn Thr Asp Gly Gly Tyr Leu Phe Ile Gly
 225 230 235 240

Leu Asn Glu Asp Lys Glu Ile Ile Gly Phe Lys Ala Glu Met Ser Asp
 245 250 255

Leu Asp Asp Leu Glu Arg Glu Ile Glu Lys Ser Ile Arg Lys Met Pro
 260 265 270

Val His His Phe Cys Met Glu Lys Lys Lys Ile Asn Tyr Ser Cys Lys
 275 280 285

Phe Leu Gly Val Tyr Asp Lys Gly Ser Leu Cys Gly Tyr Val Cys Ala
 290 295 300

Leu Arg Val Glu Arg Phe Cys Cys Ala Val Phe Ala Lys Glu Pro Asp
 305 310 315 320

Ser Trp His Val Lys Asp Asn Arg Val Met Gln Leu Thr Arg Lys Glu
 325 330 335

Trp Ile Gln Phe Met Val Glu Ala Glu Pro Lys Phe Ser Ser Ser Tyr
 340 345 350

Glu Glu Val Ile Ser Gln Ile Asn Thr Ser Leu Pro Ala Pro His Ser
 355 360 365

Trp Pro Leu Leu Glu Trp Gln Arg Gln Arg His His Cys Pro Gly Leu
 370 375 380

102

Ser Gly Arg Ile Thr Tyr Thr Pro Glu Asn Leu Cys Arg Lys Leu Phe
 385 390 395 400
 Leu Gln His Glu Gly Leu Lys Gln Leu Ile Cys Glu Glu Met Asp Ser
 405 410 415
 Val Arg Lys Gly Ser Leu Ile Phe Ser Arg Ser Trp Ser Val Asp Leu
 420 425 430
 Gly Leu Gln Glu Asn His Lys Val Leu Cys Asp Ala Leu Leu Ile Ser
 435 440 445
 Gln Asp Ser Pro Pro Val Leu Tyr Thr Phe His Met Val Gln Asp Glu
 450 455 460
 Glu Phe Lys Gly Tyr Ser Thr Gln Thr Ala Leu Thr Leu Lys Gln Lys
 465 470 475 480
 Leu Ala Lys Ile Gly Gly Tyr Thr Lys Lys Val Cys Val Met Thr Lys
 485 490 495
 Ile Phe Tyr Leu Ser Pro Glu Gly Met Thr Ser Cys Gln Tyr Asp Leu
 500 505 510
 Arg Ser Gln Val Ile Tyr Pro Glu Ser Tyr Tyr Phe Thr Arg Arg Lys
 515 520 525
 Tyr Leu Leu Lys Ala Leu Phe Lys Ala Leu Lys Arg Leu Lys Ser Leu
 530 535 540
 Arg Asp Gln Phe Ser Phe Ala Glu Asn Leu Tyr Gln Ile Ile Gly Ile
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 Asp Cys Phe Gln Lys Asn Asp Lys Lys Met Phe Lys Ser Cys Arg Arg
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 Leu Thr

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<212> DNA

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ctg gtc atc gat gtc gga gaa gtg act ctg gga gaa gaa aac aga aaa      96
Leu Val Ile Asp Val Gly Glu Val Thr Leu Gly Glu Glu Asn Arg Lys
20                               25                               30

aag cta cag aaa act cag aga gac caa gag agg gcg aga gtt ata cgg      144
Lys Leu Gln Lys Thr Gln Arg Asp Gln Glu Arg Ala Arg Val Ile Arg
35                               40                               45

gcc gcg tgt gct tta tta aac tca gga gga gga gtg att cag atg gaa      192
Ala Ala Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Gln Met Glu
50                               55                               60

atg gcc aac agg gat gag cgt ccc aca gag atg gga ctg gat tta gaa      240
Met Ala Asn Arg Asp Glu Arg Pro Thr Glu Met Gly Leu Asp Leu Glu
65                               70                               75

gaa tcc ttg aga aag ctt att cag tat cca tat ttg cag gct ttc ttt      288
Glu Ser Leu Arg Lys Leu Ile Gln Tyr Pro Tyr Leu Gln Ala Phe Phe
85                               90                               95

gag act aag caa cac gga agg tgt ttt tat att ttt gtt aaa tct tgg      336
Glu Thr Lys Gln His Gly Arg Cys Phe Tyr Ile Phe Val Lys Ser Trp
100                              105                              110

agt ggt gat cct ttc ctt aaa gat ggt tct ttc aat tcc cgc att tgc      384
Ser Gly Asp Pro Phe Leu Lys Asp Gly Ser Phe Asn Ser Arg Ile Cys
115                              120                              125

agc ctt agt tct tca tta tac tgt aga tct ggc acc tct gtg ctt cac      432
Ser Leu Ser Ser Ser Leu Tyr Cys Arg Ser Gly Thr Ser Val Leu His
130                              135                              140

atg aat tca aga cag gca ttc gat ttc ctg aag acc aag gaa aga cag      480
Met Asn Ser Arg Gln Ala Phe Asp Phe Leu Lys Thr Lys Glu Arg Gln
145                              150                              155                              160

tcc aaa tat aat ctg att aat gaa ggg tct cca cct agt aaa att atg      528
Ser Lys Tyr Asn Leu Ile Asn Glu Gly Ser Pro Pro Ser Lys Ile Met
165                              170                              175

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104

aaa gct gta tac cag aac ata tct gag tca aat cct gca tat gaa gtt	576
Lys Ala Val Tyr Gln Asn Ile Ser Glu Ser Asn Pro Ala Tyr Glu Val	
180 185 190	
ttc caa act gac act att gaa tat ggt gaa atc cta tct ttt cct gag	624
Phe Gln Thr Asp Thr Ile Glu Tyr Gly Glu Ile Leu Ser Phe Pro Glu	
195 200 205	
tct cca tcc ata gag ttt aaa cag ttc tct aca aaa cat atc caa caa	672
Ser Pro Ser Ile Glu Phe Lys Gln Phe Ser Thr Lys His Ile Gln Gln	
210 215 220	
tat gta gaa aat ata att cca gag tac atc tct gca ttt gca aac act	720
Tyr Val Glu Asn Ile Ile Pro Glu Tyr Ile Ser Ala Phe Ala Asn Thr	
225 230 235 240	
gag gga ggc tat ctt ttt att gga gtg gat gat aag agt agg aaa gtc	768
Glu Gly Gly Tyr Leu Phe Ile Gly Val Asp Asp Lys Ser Arg Lys Val	
245 250 255	
ctg gga tgt gcc aaa gaa cag gtt gac cct gac tct ttg aaa aat gta	816
Leu Gly Cys Ala Lys Glu Gln Val Asp Pro Asp Ser Leu Lys Asn Val	
260 265 270	
att gca aga gca att tct aag ttg ccc att gtt cat ttt tgc tct tca	864
Ile Ala Arg Ala Ile Ser Lys Leu Pro Ile Val His Phe Cys Ser Ser	
275 280 285	
aaa cct cgg gta gag tac agc acc aaa atc gta gaa gtg ttt tgt ggg	912
Lys Pro Arg Val Glu Tyr Ser Thr Lys Ile Val Glu Val Phe Cys Gly	
290 295 300	
aaa gag ttg tat ggc tat ctc tgt gtg att aaa gtg aag gca ttc tgt	960
Lys Glu Leu Tyr Gly Tyr Leu Cys Val Ile Lys Val Lys Ala Phe Cys	
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tgt gtg gtg ttc tcg gaa gct ccc aag tca tgg atg gtg agg gag aag	1008
Cys Val Val Phe Ser Glu Ala Pro Lys Ser Trp Met Val Arg Glu Lys	
325 330 335	
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Tyr Ile Arg Pro Leu Thr Thr Glu Glu Trp Val Glu Lys Met Met Asp	
340 345 350	
gca gat cca gag ttt cct cca gac ttt gct gag gcc ttt gag tct cag	1104
Ala Asp Pro Glu Phe Pro Pro Asp Phe Ala Glu Ala Phe Glu Ser Gln	
355 360 365	
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Leu Ser Leu Ser Asp Ser Pro Ser Leu Cys Arg Pro Val Tyr Ser Lys	
370 375 380	
aaa ggt ctg gaa cac aaa gct gat cta caa caa cat tta ttt cca gtt	1200
Lys Gly Leu Glu His Lys Ala Asp Leu Gln Gln His Leu Phe Pro Val	
385 390 395 400	
cca cca gga cat ttg gaa tgt act cca gag tcc ctc tgg aag gag ctg	1248
Pro Pro Gly His Leu Glu Cys Thr Pro Glu Ser Leu Trp Lys Glu Leu	
405 410 415	

105

tct tta cag cat gaa gga cta aag gag tta ata cac aag caa atg cga Ser Leu Gln His Glu Gly Leu Lys Glu Leu Ile His Lys Gln Met Arg 420 425 430	1296
cct ttc tcc cag gga att gtg atc ctc tct aga agc tgg gct gtg gac Pro Phe Ser Gln Gly Ile Val Ile Leu Ser Arg Ser Trp Ala Val Asp 435 440 445	1344
ctg aac ttg cag gag aag cca gga gtc atc tgt gat gct ctg ctg ata Leu Asn Leu Gln Glu Lys Pro Gly Val Ile Cys Asp Ala Leu Leu Ile 450 455 460	1392
gca cag aac agc acc ccc att ctc tac acc att ctc agg gag cag gat Ala Gln Asn Ser Thr Pro Ile Leu Tyr Thr Ile Leu Arg Glu Gln Asp 465 470 475 480	1440
gca gag ggc cag gac tac tgc act cgc acc gcc ttt act ttg aag cag Ala Glu Gly Gln Asp Tyr Cys Thr Arg Thr Ala Phe Thr Leu Lys Gln 485 490 495	1488
aag cta gtg aac atg ggg ggc tac acc ggg aag gtg tgt gtc agg gcc Lys Leu Val Asn Met Gly Gly Tyr Thr Gly Lys Val Cys Val Arg Ala 500 505 510	1536
aag gtc ctc tgc ctg agt cct gag agc agc gca gag gcc ttg gag gct Lys Val Leu Cys Leu Ser Pro Glu Ser Ser Ala Glu Ala Leu Glu Ala 515 520 525	1584
gca gtg tct ccg atg gat tac cct gcg tcc tat agc ctt gca ggc acc Ala Val Ser Pro Met Asp Tyr Pro Ala Ser Tyr Ser Leu Ala Gly Thr 530 535 540	1632
cag cac atg gaa gcc ctg ctg cag tcc ctc gtg att gtc tta ctc ggc Gln His Met Glu Ala Leu Leu Gln Ser Leu Val Ile Val Leu Leu Gly 545 550 555 560	1680
ttc agg tct ctc ttg agt gac cag ctc ggc tgt gag gtt tta aat ctg Phe Arg Ser Leu Leu Ser Asp Gln Leu Gly Cys Glu Val Leu Asn Leu 565 570 575	1728
ctc aca gcc cag cag tat gag ata ttc tcc aga agc ctc cgc aag aac Leu Thr Ala Gln Gln Tyr Glu Ile Phe Ser Arg Ser Leu Arg Lys Asn 580 585 590	1776
aga gag ttg ttt gtc cac ggc tta cct ggc tca ggg aag acc atc atg Arg Glu Leu Phe Val His Gly Leu Pro Gly Ser Gly Lys Thr Ile Met 595 600 605	1824
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106

645										650					655					
gaa	aaa	ttt	gaa	cac	att	caa	cac	atc	gtc	att	gac	gaa	gct	cag	aat	2016				
Glu	Lys	Phe	Glu	His	Ile	Gln	His	Ile	Val	Ile	Asp	Glu	Ala	Gln	Asn					
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ttc	cgt	act	gaa	gat	ggg	gac	tgg	tat	agg	aag	gca	aaa	acc	atc	act	2064				
Phe	Arg	Thr	Glu	Asp	Gly	Asp	Trp	Tyr	Arg	Lys	Ala	Lys	Thr	Ile	Thr					
			675						680			685								
cag	aga	gaa	aag	gat	tgt	cca	gga	gtt	ctc	tgg	atc	ttt	ctg	gac	tac	2112				
Gln	Arg	Glu	Lys	Asp	Cys	Pro	Gly	Val	Leu	Trp	Ile	Phe	Leu	Asp	Tyr					
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Phe	Gln	Thr	Ser	His	Leu	Gly	His	Ser	Gly	Leu	Pro	Pro	Leu	Ser	Ala					
705						710						715			720					
cag	tat	cca	aga	gaa	gag	ctc	acc	aga	gta	gtt	cgc	aat	gca	gat	gaa	2208				
Gln	Tyr	Pro	Arg	Glu	Glu	Leu	Thr	Arg	Val	Val	Arg	Asn	Ala	Asp	Glu					
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ata	gcc	gag	tac	ata	caa	caa	gaa	atg	caa	cta	att	ata	gaa	aat	cct	2256				
Ile	Ala	Glu	Tyr	Ile	Gln	Gln	Glu	Met	Gln	Leu	Ile	Ile	Glu	Asn	Pro					
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cca	att	aat	atc	ccc	cat	ggg	tat	ctg	gca	att	ctc	agt	gaa	gct	aaa	2304				
Pro	Ile	Asn	Ile	Pro	His	Gly	Tyr	Leu	Ala	Ile	Leu	Ser	Glu	Ala	Lys					
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tgg	gtt	cca	ggg	gtt	cca	ggc	aac	aca	aag	att	att	aaa	aac	ttt	act	2352				
Trp	Val	Pro	Gly	Val	Pro	Gly	Asn	Thr	Lys	Ile	Ile	Lys	Asn	Phe	Thr					
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Leu	Glu	Gln	Ile	Val	Thr	Tyr	Val	Ala	Asp	Thr	Cys	Arg	Cys	Phe	Phe					
785						790						795			800					
gaa	agg	ggc	tat	tct	cca	aag	gat	gtt	gct	gtg	ctt	gtc	agc	acc	gtg	2448				
Glu	Arg	Gly	Tyr	Ser	Pro	Lys	Asp	Val	Ala	Val	Leu	Val	Ser	Thr	Val					
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aca	gaa	gtg	gag	cag	tat	cag	tct	aag	ctc	ttg	aaa	gca	atg	agg	aag	2496				
Thr	Glu	Val	Glu	Gln	Tyr	Gln	Ser	Lys	Leu	Leu	Lys	Ala	Met	Arg	Lys					
			820						825			830								
aaa	atg	gtg	gtg	cag	ctc	agt	gat	gca	tgt	gat	atg	ttg	ggg	gtg	cac	2544				
Lys	Met	Val	Val	Gln	Leu	Ser	Asp	Ala	Cys	Asp	Met	Leu	Gly	Val	His					
			835						840			845								
att	gtg	ttg	gac	agt	gtc	cgg	cga	ttc	tca	ggc	ctg	gaa	agg	agc	ata	2592				
Ile	Val	Leu	Asp	Ser	Val	Arg	Arg	Phe	Ser	Gly	Leu	Glu	Arg	Ser	Ile					
			850						855			860								
gtg	ttt	ggg	atc	cat	cca	agg	aca	gct	gac	cca	gct	atc	tta	ccc	aat	2640				
Val	Phe	Gly	Ile	His	Pro	Arg	Thr	Ala	Asp	Pro	Ala	Ile	Leu	Pro	Asn					
865						870						875			880					
att	ctg	atc	tgt	ctg	gct	tcc	agg	gca	aaa	cag	cac	cta	tat	att	ttt	2688				

107

Ile Leu Ile Cys Leu Ala Ser Arg Ala Lys Gln His Leu Tyr Ile Phe
 885 890 895

ctg tga
 Leu

2694

<210> 49

<211> 897

<212> PRT

<213> Homo sapiens

<400> 49

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Lys Leu Gln Lys Thr Gln Arg Asp Gln Glu Arg Ala Arg Val Ile Arg
 35 40 45

Ala Ala Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Gln Met Glu
 50 55 60

Met Ala Asn Arg Asp Glu Arg Pro Thr Glu Met Gly Leu Asp Leu Glu
 65 70 75 80

Glu Ser Leu Arg Lys Leu Ile Gln Tyr Pro Tyr Leu Gln Ala Phe Phe
 85 90 95

Glu Thr Lys Gln His Gly Arg Cys Phe Tyr Ile Phe Val Lys Ser Trp
 100 105 110

Ser Gly Asp Pro Phe Leu Lys Asp Gly Ser Phe Asn Ser Arg Ile Cys
 115 120 125

Ser Leu Ser Ser Ser Leu Tyr Cys Arg Ser Gly Thr Ser Val Leu His
 130 135 140

Met Asn Ser Arg Gln Ala Phe Asp Phe Leu Lys Thr Lys Glu Arg Gln
 145 150 155 160

108

Ser Lys Tyr Asn Leu Ile Asn Glu Gly Ser Pro Pro Ser Lys Ile Met
 165 170 175

Lys Ala Val Tyr Gln Asn Ile Ser Glu Ser Asn Pro Ala Tyr Glu Val
 180 185 190

Phe Gln Thr Asp Thr Ile Glu Tyr Gly Glu Ile Leu Ser Phe Pro Glu
 195 200 205

Ser Pro Ser Ile Glu Phe Lys Gln Phe Ser Thr Lys His Ile Gln Gln
 210 215 220

Tyr Val Glu Asn Ile Ile Pro Glu Tyr Ile Ser Ala Phe Ala Asn Thr
 225 230 235 240

Glu Gly Gly Tyr Leu Phe Ile Gly Val Asp Asp Lys Ser Arg Lys Val
 245 250 255

Leu Gly Cys Ala Lys Glu Gln Val Asp Pro Asp Ser Leu Lys Asn Val
 260 265 270

Ile Ala Arg Ala Ile Ser Lys Leu Pro Ile Val His Phe Cys Ser Ser
 275 280 285

Lys Pro Arg Val Glu Tyr Ser Thr Lys Ile Val Glu Val Phe Cys Gly
 290 295 300

Lys Glu Leu Tyr Gly Tyr Leu Cys Val Ile Lys Val Lys Ala Phe Cys
 305 310 315 320

Cys Val Val Phe Ser Glu Ala Pro Lys Ser Trp Met Val Arg Glu Lys
 325 330 335

Tyr Ile Arg Pro Leu Thr Thr Glu Glu Trp Val Glu Lys Met Met Asp
 340 345 350

Ala Asp Pro Glu Phe Pro Pro Asp Phe Ala Glu Ala Phe Glu Ser Gln
 355 360 365

Leu Ser Leu Ser Asp Ser Pro Ser Leu Cys Arg Pro Val Tyr Ser Lys
 370 375 380

Lys Gly Leu Glu His Lys Ala Asp Leu Gln Gln His Leu Phe Pro Val
 385 390 395 400

109

Pro Pro Gly His Leu Glu Cys Thr Pro Glu Ser Leu Trp Lys Glu Leu
405 410 415

Ser Leu Gln His Glu Gly Leu Lys Glu Leu Ile His Lys Gln Met Arg
420 425 430

Pro Phe Ser Gln Gly Ile Val Ile Leu Ser Arg Ser Trp Ala Val Asp
435 440 445

Leu Asn Leu Gln Glu Lys Pro Gly Val Ile Cys Asp Ala Leu Leu Ile
450 455 460

Ala Gln Asn Ser Thr Pro Ile Leu Tyr Thr Ile Leu Arg Glu Gln Asp
465 470 475 480

Ala Glu Gly Gln Asp Tyr Cys Thr Arg Thr Ala Phe Thr Leu Lys Gln
485 490 495

Lys Leu Val Asn Met Gly Gly Tyr Thr Gly Lys Val Cys Val Arg Ala
500 505 510

Lys Val Leu Cys Leu Ser Pro Glu Ser Ser Ala Glu Ala Leu Glu Ala
515 520 525

Ala Val Ser Pro Met Asp Tyr Pro Ala Ser Tyr Ser Leu Ala Gly Thr
530 535 540

Gln His Met Glu Ala Leu Leu Gln Ser Leu Val Ile Val Leu Leu Gly
545 550 555 560

Phe Arg Ser Leu Leu Ser Asp Gln Leu Gly Cys Glu Val Leu Asn Leu
565 570 575

Leu Thr Ala Gln Gln Tyr Glu Ile Phe Ser Arg Ser Leu Arg Lys Asn
580 585 590

Arg Glu Leu Phe Val His Gly Leu Pro Gly Ser Gly Lys Thr Ile Met
595 600 605

Ala Met Lys Ile Met Glu Lys Ile Arg Asn Val Phe His Cys Glu Ala
610 615 620

His Arg Ile Leu Tyr Val Cys Glu Asn Gln Pro Leu Arg Asn Phe Ile

110

625	630	635	640
Ser Asp Arg Asn Ile Cys Arg Ala Glu Thr Arg Glu Thr Phe Leu Arg	645	650	655
Glu Lys Phe Glu His Ile Gln His Ile Val Ile Asp Glu Ala Gln Asn	660	665	670
Phe Arg Thr Glu Asp Gly Asp Trp Tyr Arg Lys Ala Lys Thr Ile Thr	675	680	685
Gln Arg Glu Lys Asp Cys Pro Gly Val Leu Trp Ile Phe Leu Asp Tyr	690	695	700
Phe Gln Thr Ser His Leu Gly His Ser Gly Leu Pro Pro Leu Ser Ala	705	710	715
Gln Tyr Pro Arg Glu Glu Leu Thr Arg Val Val Arg Asn Ala Asp Glu	725	730	735
Ile Ala Glu Tyr Ile Gln Gln Glu Met Gln Leu Ile Ile Glu Asn Pro	740	745	750
Pro Ile Asn Ile Pro His Gly Tyr Leu Ala Ile Leu Ser Glu Ala Lys	755	760	765
Trp Val Pro Gly Val Pro Gly Asn Thr Lys Ile Ile Lys Asn Phe Thr	770	775	780
Leu Glu Gln Ile Val Thr Tyr Val Ala Asp Thr Cys Arg Cys Phe Phe	785	790	795
Glu Arg Gly Tyr Ser Pro Lys Asp Val Ala Val Leu Val Ser Thr Val	805	810	815
Thr Glu Val Glu Gln Tyr Gln Ser Lys Leu Leu Lys Ala Met Arg Lys	820	825	830
Lys Met Val Val Gln Leu Ser Asp Ala Cys Asp Met Leu Gly Val His	835	840	845
Ile Val Leu Asp Ser Val Arg Arg Phe Ser Gly Leu Glu Arg Ser Ile	850	855	860

111

Val Phe Gly Ile His Pro Arg Thr Ala Asp Pro Ala Ile Leu Pro Asn
 865 870 875 880

Ile Leu Ile Cys Leu Ala Ser Arg Ala Lys Gln His Leu Tyr Ile Phe
 885 890 895

Leu

<210> 50

<211> 1074

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(1071)

<223>

<400> 50

atg gag agt ctc aag act gat act gaa atg ccg tat cct gag gta ata 48
 Met Glu Ser Leu Lys Thr Asp Thr Glu Met Pro Tyr Pro Glu Val Ile
 1 5 10 15

gta gat gtg ggc aga gtg att ttt gga gaa gaa aac agg aag aag atg 96
 Val Asp Val Gly Arg Val Ile Phe Gly Glu Glu Asn Arg Lys Lys Met
 20 25 30

acc aac agc tgt ttg aaa aga tct gag aat tct aga att atc cgg gct 144
 Thr Asn Ser Cys Leu Lys Arg Ser Glu Asn Ser Arg Ile Ile Arg Ala
 35 40 45

ata tgt gca ctg tta aat tct gga ggt ggt gtg atc aaa gca gag att 192
 Ile Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Lys Ala Glu Ile
 50 55 60

gat gat aaa acc tat agt tac caa tgc cat ggg ctg gga cag gat ttg 240
 Asp Asp Lys Thr Tyr Ser Tyr Gln Cys His Gly Leu Gly Gln Asp Leu
 65 70 75 80

gaa act tct ttt caa aag ctc ctt cct tca ggt tca cag aaa tac ctt 288
 Glu Thr Ser Phe Gln Lys Leu Leu Pro Ser Gly Ser Gln Lys Tyr Leu
 85 90 95

gac tac atg cag cag ggg cac aat ctc ctg att ttt gtg aag tca tgg 336
 Asp Tyr Met Gln Gln Gly His Asn Leu Leu Ile Phe Val Lys Ser Trp

112

100										105					110					
agc	cca	gat	gtt	ttc	agc	ctt	cca	cta	agg	att	tgc	agc	ttg	cgc	tcc	384				
Ser	Pro	Asp	Val	Phe	Ser	Leu	Pro	Leu	Arg	Ile	Cys	Ser	Leu	Arg	Ser					
115					120					125										
aat	ttg	tat	cgg	aga	gat	gtg	act	tct	gct	atc	aac	ttg	agt	gct	agc	432				
Asn	Leu	Tyr	Arg	Arg	Asp	Val	Thr	Ser	Ala	Ile	Asn	Leu	Ser	Ala	Ser					
130					135					140										
agt	gcc	ctg	gag	ctt	ctc	aga	gag	aag	ggg	ttt	aga	gcc	caa	aga	gga	480				
Ser	Ala	Leu	Glu	Leu	Leu	Arg	Glu	Lys	Gly	Phe	Arg	Ala	Gln	Arg	Gly					
145					150					155					160					
aga	cca	agg	gtg	aag	aag	ttg	cat	cct	cag	cag	gtt	ctc	aat	aga	tgc	528				
Arg	Pro	Arg	Val	Lys	Lys	Leu	His	Pro	Gln	Gln	Val	Leu	Asn	Arg	Cys					
165					170					175										
att	cag	gaa	gag	gaa	gat	atg	agg	ata	ttg	gcc	tca	gaa	ttt	ttt	aaa	576				
Ile	Gln	Glu	Glu	Glu	Asp	Met	Arg	Ile	Leu	Ala	Ser	Glu	Phe	Phe	Lys					
180					185					190										
aag	gac	aaa	ctc	atg	tat	aag	gag	aaa	ctc	aac	ttt	act	gag	tca	aca	624				
Lys	Asp	Lys	Leu	Met	Tyr	Lys	Glu	Lys	Leu	Asn	Phe	Thr	Glu	Ser	Thr					
195					200					205										
cat	gtt	gaa	ttt	aaa	agg	ttc	acc	acc	aaa	aaa	gtc	ata	cct	cgg	att	672				
His	Val	Glu	Phe	Lys	Arg	Phe	Thr	Thr	Lys	Lys	Val	Ile	Pro	Arg	Ile					
210					215					220										
aag	gaa	atg	ctg	cct	cat	tat	gtt	tct	gca	ttt	gcc	aac	act	caa	ggg	720				
Lys	Glu	Met	Leu	Pro	His	Tyr	Val	Ser	Ala	Phe	Ala	Asn	Thr	Gln	Gly					
225					230					235					240					
gga	tat	gtc	ctc	att	ggg	gtg	gat	gat	aag	agc	aaa	gaa	gtg	gtt	gga	768				
Gly	Tyr	Val	Leu	Ile	Gly	Val	Asp	Asp	Lys	Ser	Lys	Glu	Val	Val	Gly					
245					250					255										
tgt	aag	tgg	gaa	aaa	gtg	aat	cct	gac	tta	cta	aaa	aaa	gaa	atc	gaa	816				
Cys	Lys	Trp	Glu	Lys	Val	Asn	Pro	Asp	Leu	Leu	Lys	Lys	Glu	Ile	Glu					
260					265					270										
aac	tgc	ata	gaa	aaa	ttg	cct	aca	ttc	cac	ttc	tgc	tgt	gag	aag	cca	864				
Asn	Cys	Ile	Glu	Lys	Leu	Pro	Thr	Phe	His	Phe	Cys	Cys	Glu	Lys	Pro					
275					280					285										
aag	gta	aat	ttc	act	aca	aaa	atc	ctg	aat	gtg	tac	caa	aaa	gat	gtc	912				
Lys	Val	Asn	Phe	Thr	Thr	Lys	Ile	Leu	Asn	Val	Tyr	Gln	Lys	Asp	Val					
290					295					300										
ctg	gat	ggt	tat	gtc	tgt	gtg	att	caa	gtg	gag	ccc	ttc	tgt	tgc	gtg	960				
Leu	Asp	Gly	Tyr	Val	Cys	Val	Ile	Gln	Val	Glu	Pro	Phe	Cys	Cys	Val					
305					310					315					320					
gtg	ttt	gca	gag	gcc	cca	gat	tcc	tgg	atc	atg	aaa	gac	aat	tct	gtc	1008				
Val	Phe	Ala	Glu	Ala	Pro	Asp	Ser	Trp	Ile	Met	Lys	Asp	Asn	Ser	Val					
325					330					335										
aca	cgg	ctg	aca	gct	gag	cag	tgg	gtg	gtc	atg	atg	ctg	gat	act	cag	1056				

113

Thr Arg Leu Thr Ala Glu Gln Trp Val Val Met Met Leu Asp Thr Gln
 340 345 350

tca ggt aaa ggg aag tga
 Ser Gly Lys Gly Lys
 355

1074

<210> 51

<211> 357

<212> PRT

<213> Homo sapiens

<400> 51

Met Glu Ser Leu Lys Thr Asp Thr Glu Met Pro Tyr Pro Glu Val Ile
 1 5 10 15

Val Asp Val Gly Arg Val Ile Phe Gly Glu Glu Asn Arg Lys Lys Met
 20 25 30

Thr Asn Ser Cys Leu Lys Arg Ser Glu Asn Ser Arg Ile Ile Arg Ala
 35 40 45

Ile Cys Ala Leu Leu Asn Ser Gly Gly Gly Val Ile Lys Ala Glu Ile
 50 55 60

Asp Asp Lys Thr Tyr Ser Tyr Gln Cys His Gly Leu Gly Gln Asp Leu
 65 70 75 80

Glu Thr Ser Phe Gln Lys Leu Leu Pro Ser Gly Ser Gln Lys Tyr Leu
 85 90 95

Asp Tyr Met Gln Gln Gly His Asn Leu Leu Ile Phe Val Lys Ser Trp
 100 105 110

Ser Pro Asp Val Phe Ser Leu Pro Leu Arg Ile Cys Ser Leu Arg Ser
 115 120 125

Asn Leu Tyr Arg Arg Asp Val Thr Ser Ala Ile Asn Leu Ser Ala Ser
 130 135 140

Ser Ala Leu Glu Leu Leu Arg Glu Lys Gly Phe Arg Ala Gln Arg Gly
 145 150 155 160

114

Arg Pro Arg Val Lys Lys Leu His Pro Gln Gln Val Leu Asn Arg Cys
 165 170 175

Ile Gln Glu Glu Glu Asp Met Arg Ile Leu Ala Ser Glu Phe Phe Lys
 180 185 190

Lys Asp Lys Leu Met Tyr Lys Glu Lys Leu Asn Phe Thr Glu Ser Thr
 195 200 205

His Val Glu Phe Lys Arg Phe Thr Thr Lys Lys Val Ile Pro Arg Ile
 210 215 220

Lys Glu Met Leu Pro His Tyr Val Ser Ala Phe Ala Asn Thr Gln Gly
 225 230 235 240

Gly Tyr Val Leu Ile Gly Val Asp Asp Lys Ser Lys Glu Val Val Gly
 245 250 255

Cys Lys Trp Glu Lys Val Asn Pro Asp Leu Leu Lys Lys Glu Ile Glu
 260 265 270

Asn Cys Ile Glu Lys Leu Pro Thr Phe His Phe Cys Cys Glu Lys Pro
 275 280 285

Lys Val Asn Phe Thr Thr Lys Ile Leu Asn Val Tyr Gln Lys Asp Val
 290 295 300

Leu Asp Gly Tyr Val Cys Val Ile Gln Val Glu Pro Phe Cys Cys Val
 305 310 315 320

Val Phe Ala Glu Ala Pro Asp Ser Trp Ile Met Lys Asp Asn Ser Val
 325 330 335

Thr Arg Leu Thr Ala Glu Gln Trp Val Val Met Met Leu Asp Thr Gln
 340 345 350

Ser Gly Lys Gly Lys
 355

<210> 52

<211> 807

<212> DNA

115

<213> Mus musculus

<220>

<221> CDS

<222> (1) .. (804)

<223>

<400> 52

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Met Leu Phe Val Lys Gln Ser Asp Lys Gly Ile Asn Ser Lys Arg Arg	
1 5 10 15	
agc aaa gcc agg agg ctg aag ctt ggc ctg cca gga ccc cca ggg cca	96
Ser Lys Ala Arg Arg Leu Lys Leu Gly Leu Pro Gly Pro Pro Gly Pro	
20 25 30	
cca ggt cct cag ggc ccc cca ggc ccc ttt atc cca tct gag gtt ctg	144
Pro Gly Pro Gln Gly Pro Pro Gly Pro Phe Ile Pro Ser Glu Val Leu	
35 40 45	
ctg aag gag ttc cag ctg ttg ctg aaa ggc gca gta cgg cag cga gag	192
Leu Lys Glu Phe Gln Leu Leu Leu Lys Gly Ala Val Arg Gln Arg Glu	
50 55 60	
agc cat ctg gag cac tgc acc agg gat ctc act aca cca gcc tcg ggt	240
Ser His Leu Glu His Cys Thr Arg Asp Leu Thr Thr Pro Ala Ser Gly	
65 70 75 80	
agc cct tcc cgt gtc cca gcc gcc cag gag ctt gat agc cag gac cca	288
Ser Pro Ser Arg Val Pro Ala Ala Gln Glu Leu Asp Ser Gln Asp Pro	
85 90 95	
ggg gca ttg tta gct ctg ctg gct gcg acc ttg gcc cag ggc ccg cgg	336
Gly Ala Leu Leu Ala Leu Leu Ala Ala Thr Leu Ala Gln Gly Pro Arg	
100 105 110	
gca cca cgt gtg gag gcc gca ttc cac tgt cgc ttg cgc cgg gat gtg	384
Ala Pro Arg Val Glu Ala Ala Phe His Cys Arg Leu Arg Arg Asp Val	
115 120 125	
cag gtg gat cgg cgt gcg ttg cac gag ctt ggg atc tac tac ctg ccc	432
Gln Val Asp Arg Arg Ala Leu His Glu Leu Gly Ile Tyr Tyr Leu Pro	
130 135 140	
gaa gtt gag gga gcc ttc cac cgg ggc cca ggc ttg aat ctg acc agc	480
Glu Val Glu Gly Ala Phe His Arg Gly Pro Gly Leu Asn Leu Thr Ser	
145 150 155 160	
ggc cag tac acc gca cct gtg gct ggc ttc tat gcg ctt gct gcc act	528
Gly Gln Tyr Thr Ala Pro Val Ala Gly Phe Tyr Ala Leu Ala Ala Thr	
165 170 175	

116

ctg cac gtg gca ctc acc gag cag cca aga aag gga cca aca cga ccc 576
 Leu His Val Ala Leu Thr Glu Gln Pro Arg Lys Gly Pro Thr Arg Pro
 180 185 190

cgg gat cgt ctg cgc ctg ctg atc tgc atc cag tct ctc tgt cag cac 624
 Arg Asp Arg Leu Arg Leu Leu Ile Cys Ile Gln Ser Leu Cys Gln His
 195 200 205

aat gcc tcc ctg gag act gtg atg ggg ctg gag aac agc agc gag ctc 672
 Asn Ala Ser Leu Glu Thr Val Met Gly Leu Glu Asn Ser Ser Glu Leu
 210 215 220

ttc acc atc tca gta aat ggt gtc ctc tat cta cag gca gga cac tac 720
 Phe Thr Ile Ser Val Asn Gly Val Leu Tyr Leu Gln Ala Gly His Tyr
 225 230 235 240

act tct gtc ttc ttg gac aat gcc agc ggc tcc tcc ctc acg gta cgc 768
 Thr Ser Val Phe Leu Asp Asn Ala Ser Gly Ser Ser Leu Thr Val Arg
 245 250 255

agt ggc tct cac ttc agt gct atc ctc ctg ggc ctg tga 807
 Ser Gly Ser His Phe Ser Ala Ile Leu Leu Gly Leu
 260 265

<210> 53

<211> 268

<212> PRT

<213> Mus musculus

<400> 53

Met Leu Phe Val Lys Gln Ser Asp Lys Gly Ile Asn Ser Lys Arg Arg
 1 5 10 15

Ser Lys Ala Arg Arg Leu Lys Leu Gly Leu Pro Gly Pro Pro Gly Pro
 20 25 30

Pro Gly Pro Gln Gly Pro Pro Gly Pro Phe Ile Pro Ser Glu Val Leu
 35 40 45

Leu Lys Glu Phe Gln Leu Leu Leu Lys Gly Ala Val Arg Gln Arg Glu
 50 55 60

Ser His Leu Glu His Cys Thr Arg Asp Leu Thr Thr Pro Ala Ser Gly
 65 70 75 80

Ser Pro Ser Arg Val Pro Ala Ala Gln Glu Leu Asp Ser Gln Asp Pro
 85 90 95

117

Gly Ala Leu Leu Ala Leu Leu Ala Ala Thr Leu Ala Gln Gly Pro Arg
100 105 110

Ala Pro Arg Val Glu Ala Ala Phe His Cys Arg Leu Arg Arg Asp Val
115 120 125

Gln Val Asp Arg Arg Ala Leu His Glu Leu Gly Ile Tyr Tyr Leu Pro
130 135 140

Glu Val Glu Gly Ala Phe His Arg Gly Pro Gly Leu Asn Leu Thr Ser
145 150 155 160

Gly Gln Tyr Thr Ala Pro Val Ala Gly Phe Tyr Ala Leu Ala Ala Thr
165 170 175

Leu His Val Ala Leu Thr Glu Gln Pro Arg Lys Gly Pro Thr Arg Pro
180 185 190

Arg Asp Arg Leu Arg Leu Leu Ile Cys Ile Gln Ser Leu Cys Gln His
195 200 205

Asn Ala Ser Leu Glu Thr Val Met Gly Leu Glu Asn Ser Ser Glu Leu
210 215 220

Phe Thr Ile Ser Val Asn Gly Val Leu Tyr Leu Gln Ala Gly His Tyr
225 230 235 240

Thr Ser Val Phe Leu Asp Asn Ala Ser Gly Ser Ser Leu Thr Val Arg
245 250 255

Ser Gly Ser His Phe Ser Ala Ile Leu Leu Gly Leu
260 265

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